

Perinatal Transmission and Outcome of Neonates Born to SARS-CoV-2-Positive Mothers: The Experience of 2 Highly Endemic Italian Regions

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Keywords

Coronavirus · SARS-CoV-2 · Vertical transmission · COVID-19 · Newborn · Neonates

Abstract

Introduction: COVID-19 is the disease caused by the novel coronavirus SARS-CoV-2, responsible of the pandemic declared in March 2020 and still ongoing. COVID-19 affects all ages but presents less complications and fatalities in children. Neonatal infections have rarely been reported worldwide, and vertical transmission is uncertain. **Methods:** We conducted a prospective cohort study of all infants born to SARS-CoV-2-positive mothers admitted to 2 hospitals in South (Bari) and North (Varese) of Italy from April to December 2020. A molecular nasopharyngeal swab for SARS-CoV-2 using a reverse transcriptase polymerase chain reaction was made at birth for all enrolled newborns to evaluate vertical transmission of infection. We also evaluated postnatal transmission with a second nasopharyngeal swab made at 1 month of life and described maternal and neonatal clinical findings and short-term outcomes. **Results:** 176/179 (97%)

newborns were SARS-CoV-2 negative at birth and 151/156 (97%) infants were still negative at 1 month of life. All newborns were asymptomatic. Seventy percent of newborns were breastfed during hospitalization. At 1 month of life, 76% of infants were breastfed. **Conclusion:** According to our results, vertical and perinatal infection is very rare. Breast-feeding does not increase the risk of COVID-19 and should be encouraged.

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Introduction

COVID-19 is a worldwide emerging infectious disease caused by the novel coronavirus SARS-CoV-2 [1], responsible of the ongoing pandemic, declared by the WHO on March 12, 2020 [2]. Male sex, old age, and some comorbidities, such as diabetes, hypertension, and obesity, are the most significant risk factors for increased incidence and fatality rates of COVID-19 [3].

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COVID-19 in children is much rarer and less severe than in adults [4], although fatalities and multisystem inflammatory syndrome SARS-CoV-2 related have been described [5]. Data on newborns are still limited. According to a recent meta-analysis, the mother and newborn usually have a mild course of infection, whilst a severe form occurred in 7–11% of women and preterm birth occurred in 29.7% or 16% based on case series or observational studies [6]. SARS-CoV-2 infection was confirmed in 11% of neonates born to infected mothers and only in 2% with vertical transmission, and fever was the most frequent symptom (40%), followed by shortness of breath (28%) and vomiting (24%); 20% of neonates were asymptomatic [6].

The aims of this study were to evaluate SARS-CoV-2 perinatal transmission and describe maternal and neonatal clinical findings and short-term outcomes in a large Italian cohort from 2 high epidemic areas. Moreover, we would like to assess if some possible differences between the 2 hospitals regarding daily standard care (rooming-in and rate of breastfeeding), due to different logistical characteristics and problems (i.e., hospital overcrowding due to pandemic), have a role in the incidence of SARS-CoV-2 and could modify the infection risk of the newborns.

Materials and Methods

A prospective cohort study of all neonates born to SARS-CoV-2-positive mothers admitted to 2 large secondary-level Neonatology and Neonatal Intensive Care Units (NICU) in South (Bari) and North (Varese) of Italy, from April to December 2020, was conducted. A molecular nasopharyngeal swab for SARS-CoV-2 using a reverse transcriptase polymerase chain reaction (NP-s RT-PCR) was performed on the day of admission to the Labor and Delivery ward, in all pregnant women. All SARS-CoV-2-positive women were isolated with personal protective equipment and indications for hand hygiene. Symptoms of COVID-19 were recorded. An NP-s RT-PCR was performed in all newborns to SARS-CoV-2-positive mothers at birth in the delivery room and analyzed at the local Molecular and Microbiology Laboratories.

Rooming-in and breastfeeding were promoted, after carefully instructing the mothers to wear a surgical mask, wash hands and breast often, and maintain the baby at least 2 m away, except during breastfeeding. Neonates requiring higher level of care or to mothers with COVID-19, unable to care for her baby for medical reasons, were admitted to the Neo/NICU. Clinical data were collected, with particular attention to gestational age, delivery mode, Apgar score, type of feeding, need for admission in Neo/NICU, length of hospitalization, and results of SARS-CoV-2 tests.

According to recommendations to reduce infection risk [7], both women and neonates, if clinically stable, were sent home 24 h after vaginal delivery or 48 h after C-section that were 24 h earlier than prior COVID-19 pandemic. After discharge, telephone interviews were conducted by an experienced physician. All neo-

nates underwent a medical examination to evaluate growth and clinical status and received a second NP-s RT-PCR at 1 month of age. Further prospective follow-up is ongoing. An ethics committee approved the study (No. 46322; April 7, 2020). Informed consent was signed by all participant mothers.

Statistical Analysis

A preliminary description of data was made by descriptive statistics. Comparisons between the mothers' data recorded in the 2 Italian hospitals were done by the independent samples Student *t* test for quantitative variables and χ^2 and Fisher exact test (when more opportune) to compare proportions. The same evaluations were performed for newborn data, and APGAR score comparisons were done by the median test. The evaluation of breastfeeding and rooming-in as potential risk factors was done by risk ratio calculation.

Results

Out of 2,782 pregnant women admitted to Bari and Varese hospitals from April to December 2020, 179 (6%) resulted SARS-CoV-2 positive: 16% had symptoms of COVID-19 and 3% were admitted to ICU, and no death occurred. Among 181 enrolled neonates, 5 (2.7%) were positive at birth. At 1 month of age, 156 (86%) were retested and 151 (97%) were negative (Fig. 1). In 25 cases (14%), parents refused to repeat NP-s RT-PCR; all these infants were negative at birth and remained asymptomatic at 1 month of age. All positive newborns were asymptomatic at birth and at 1 month of age.

Rooming-in and breastfeeding were promoted and did not increase the rate of SARS-CoV-2 infection with an RR = 0.464 (95% CI: 0.12–1.79) and RR = 1.43 (95% CI: 0.16–33.45), respectively. Rooming-in was possible for 68% of neonates; 70% of neonates were breastfed at discharge and 76% at 1 month of life. We evaluated data from 2 Italian hospitals (Table 1).

Data from Bari

Mothers

Out of 757 pregnant women admitted, 90 (12%) were SARS-CoV-2 positive, and of them, 70 (78%) were asymptomatic and 20 (22%) affected by COVID-19: anosmia and ageusia, cough, dyspnea, fever, and rhinitis were the most common symptoms, occurring in 7 (8%), 7 (8%), 6 (7%), 5 (5%), and 5 (5%) women, respectively. Four women (5%) developed respiratory failure after delivery and were transferred to the Intensive Care Unit

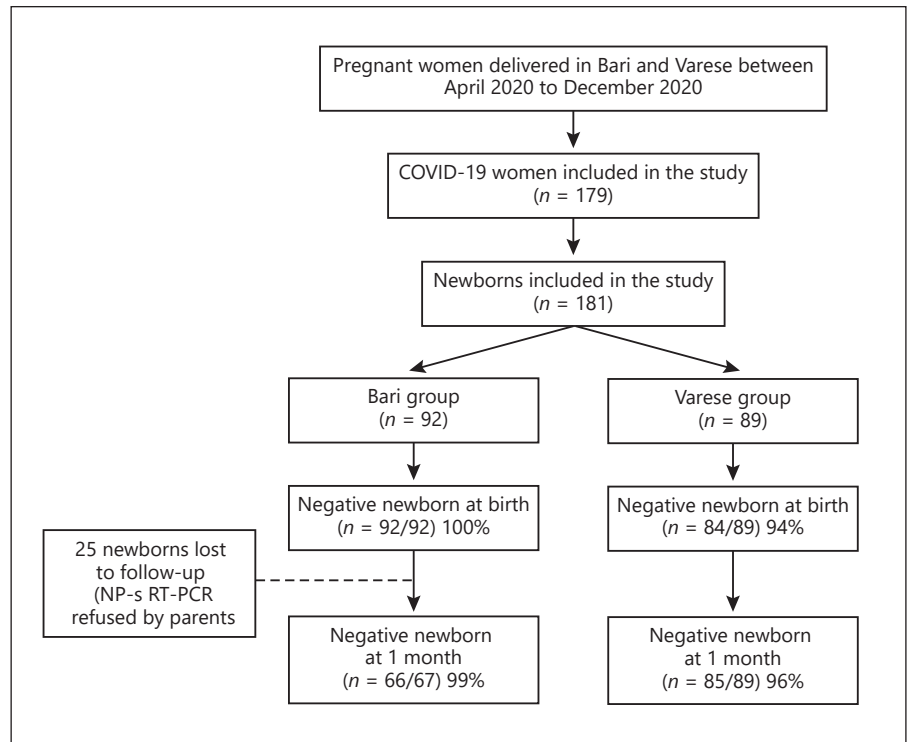


Fig. 1. Flowchart of study participants.

Table 1. Demographic and clinical characteristics of maternal and neonatal populations

Characteristics	All	Bari	Varese	<i>p</i> value
SARS-CoV-2-positive mothers, <i>n</i>	179	90	89	
Cesarean section, <i>n</i> (%)	50 (28)	34 (38)	16 (18)	0.005
COVID symptoms, <i>n</i> (%)	27 (15)	20 (23)	7 (8)	0.01
Admission to ICU, <i>n</i> (%)	4 (3)	4 (4.5)	0 (0)	0.12
Newborns, <i>n</i>	181	92	89	
GA, mean (SD), weeks	39 (±2)	39 (±1.6)	39 (±2.4)	0.422
Preterm, <i>n</i> (%)	20 (11)	7 (8)	13 (15)	0.133
Birth weight, m (SD), g	3,161 (±521)	3,237 (±443)	3,083 (±584)	0.046
SGA/AGA/LGA				
SGA, <i>n</i> (%)	17 (9)	6 (7)	11 (12)	0.275
AGA, <i>n</i> (%)	155 (86)	80 (87)	75 (84)	
LGA, <i>n</i> (%)	9 (5)	6 (7)	3 (3)	
Females, <i>n</i> (%)	90 (50)	53 (58)	37 (42)	0.031
Apgar score at 1 min, median (Q ₁ –Q ₃)	9 (9–9)	9 (9–9)	9 (9–9)	0.142
Apgar score at 5 min, median (Q ₁ –Q ₃)	10 (9–10)	10 (9–10)	10 (10–10)	0.26
Negative NP-s RT-PCR at birth, <i>n</i> (%)	176 (97)	92 (100)	84 (94)	0.027
Newborns tested at 1 month, <i>n</i> (%)	156 (86)	67 (73)	89 (100)	<0.001
Negative NP-s RT-PCR at 1 month, <i>n</i> (%)	151 (97)	66/67 (99)	85/89 (96)	0.39
Breastfeeding during hospitalization, <i>n</i> (%)	127 (70)	44 (48)	83 (93)	<0.001
Breastfeeding at 1 month, <i>n</i> (%)	137 (76)	70 (76)	67 (75)	0.429
Rooming-in, <i>n</i> (%)	123 (68)	44 (48)	79 (89)	<0.001

GA, gestational age.

(ICU) and treated with oxygen therapy, broad-spectrum antimicrobial therapy (azithromycin), and corticosteroids (deltacortene); 3 of them also received heparin, and none was given hydroxychloroquine or an antiviral agent. No woman received antepartum therapy but symptomatic therapy (paracetamol); none required mechanical ventilation, and no maternal death occurred.

Fifty-six (62%) women had vaginal delivery and 34 (38%) C-section, urgent in 13/34 (38%), including 3 out of 4 cases of severe COVID-19. Most of the C-sections occurred for indications other than SARS-CoV-2 infection.

Neonates

Ninety-two infants were born to 90 positive mothers; all were tested by NP-s RT-PCR at birth and were negative for SARS-CoV-2. Gestational age ranged between 33 + 6 and 42 + 0 weeks (39 ± 1.6); 7 (8%) were preterm. Birth weight ranged between 2,045 g and 4,580 g ($3,237 \pm 443$ g); 6 (6.5%) newborns were small for gestational age and 6 (7%) large for gestational age. Median Apgar score at 1 and 5 min was 9 and 10, respectively. None required resuscitation, according to the Neonatal Resuscitation Guidelines [8].

Rooming-in was realized in 44 (48%) and 48 (52%) were admitted to Neo/NICU. 41/48 neonates were admitted because of hospital overcrowding in the Obstetrics ward, even if they have good clinical conditions.

One late-preterm newborn from urgent C-section because of fetal bradycardia developed respiratory distress syndrome and was admitted for 9 days. Two late-preterm twins were admitted for 29 days and 1 term newborn for 25 days because of maternal COVID-19 pneumonia. Two late-preterm newborns were admitted for transient hypoglycemia for 4 days. One late-preterm newborn with VACTERL syndrome is currently still hospitalized after 85 days.

Excluding this complicated case, hospitalization ranged from 1 to 60 days (4.8 ± 8.4). Forty-four (48%) neonates were breastfed at discharge and 70 (76%) at 1 month of age. 67/92 (73%) neonates repeated NP-s RT-PCR at 1 month of age; 25 (27%) were not re-tested because of parental refusal (20, 22.2%) or need of quarantine (5, 5.5% of total population).

Only 1 newborn was positive but asymptomatic. His mother was still positive and asymptomatic 1 month after delivery and then turned negative 2 weeks later. Breastfeeding and rooming-in were promoted, even if not highly performed (48%), and did not increase the rate of SARS-CoV-2 infection; relative risk, respectively, of 2.18 (95% CI: 0.21–22.93) and 2.3 (95% CI: 0.21–16.5) was not statistically significant.

Data from Varese

Mothers

Out of 2,025 pregnant women admitted, 89 (4%) resulted SARS-CoV-2 positive. Seven (8.4%) positive women had COVID-19: 5 reported respiratory symptoms (2 cough and 3 pneumonia) and 2 only fever. Infected women received only symptomatic therapy (paracetamol) antepartum. Only 1 woman developed respiratory failure with oxygen need and was treated with steroids and azithromycin; no maternal deaths were reported. Most women (73.8%) had vaginal delivery and 16 (18%) C-sections, of which 6 (38%) urgent.

Neonates

Eighty-nine neonates were born to 89 positive mothers, and all were tested by NP-s RT-PCR at birth; 84/89 (94%) were SARS-CoV-2 negative, and all newborns were asymptomatic. Gestational age ranged between 28 + 3 and 41 + 6 weeks (39 ± 2.4); 13 (15%) were preterm. Birth weight ranged between 1,300 g and 4,260 g ($3,083 \pm 584$ g); 11 (12%) were small for gestational age and 3 (3%) large for gestational age. Median Apgar score at 1 and 5 min was 9 and 10, respectively.

Two very low birth weight preterm newborns, born at 28 weeks from urgent C-section because of fetal tachycardia, required neonatal resuscitation [8] and developed respiratory distress syndrome. The other 7 preterm newborns had no complications.

One full-term neonate, negative at birth, was readmitted after 9 days because of vomiting and abdominal distension. Necrotizing enterocolitis was diagnosed, with need of broad-spectrum antibiotics and intestinal resection. He remained negative when operated and at 1 month of age and still in NICU after 80 days.

Excluding this complicated case, hospitalization ranged from 2 to 48 days (5.8 ± 1.4). Rooming-in was possible in 79 (89%); breastfeeding at discharge was achieved in 83 (93%) and in 67 (75%) at 1 month of age.

NP-s RT-PCR at 1 month of age was done in all neonates. Four (4.8%) resulted positive but asymptomatic: 2 (2.4%) were already positive at birth, and their mothers were negative 14 days after delivery; 2 (2.4%) turned positive probably due to environmental transmission, and their mothers were still positive and paucisymptomatic (anosmia/ageusia) after 1 month and then turned negative after 2 weeks. Breastfeeding and rooming-in were promoted and achieved in 93% and 89% of cases and did not increase the rate of SARS-CoV-2 infection; relative risk, respectively, of 0.22 (95% CI: 0.03–1.78) and 0.74 (95% CI: 0.09–5.81) was not statistically significant.

Comparison of the 2 Hospitals

Comparing data from the 2 hospitals, some differences emerge in relation to both mothers and newborns. Symptomatic positive mothers were more numerous in Bari, 20/90 (23%) versus 7/89 (8%) in Varese ($p = 0.01$), as well as the rate of C-sections, 34/90 (38%) in Bari versus 16/89 (18%) in Varese ($p = 0.005$). As for the newborns, birth weight was slightly lower in Varese ($3,083 \pm 584$ g) than in Bari ($3,237 \pm 443$ g), $p = 0.046$.

Regarding SARS-CoV-2 tests at birth, all newborns (92/92, 100%) were negative in Bari, whilst in Varese, 84/89 (94%) were negative, $p = 0.027$. The number of infants re-tested at 1 month of life was higher in Varese, 89/89 (100%) versus 67/92 (73%) in Bari, $p < 0.001$, but no significant differences emerged in relation to the results of NP-s RT-PCR.

Rooming-in was performed in 79/89 (89%) in Varese versus 44/92 (48%) in Bari ($p < 0.001$), and breastfeeding during hospitalization was achieved in 83/89 (93%) newborns in Varese compared to 44/92 (48%) in Bari ($p < 0.001$). This difference, however, was no longer evident in relation to the breastfeeding rate at 1 month of age.

Discussion

Evidence of the best perinatal management and post-natal outcome of infants born to SARS-CoV-2-positive mothers is still limited. The risk of vertical transmission appeared to be very low, and only rare cases have been reported worldwide [9]. The placenta seems to prevent SARS-CoV-2 transfer to the fetus, although the protective factors still need to be fully clarified [7].

In our study, all newborns (92/92, 100%) were SARS-CoV-2 negative in Bari and 84/89 (94%) negative in Varese with a slight difference between the 2 centers, but total results are consistent with a recent review that showed that 92% of newborns to SARS-CoV-2-infected mothers are negative at birth [10]. Some studies demonstrated a very low incidence of neonatal infection and COVID-19 symptoms during the first month of life [11].

Our results are consistent with a US retrospective cohort of 101 neonates born to SARS-CoV-2-infected mothers, in which 2% were positive but none had clinical evidence of COVID-19, although most infants (90%) were breastfed. Only half of these neonates were followed up for 2 weeks, and all remained healthy [12].

A recent review [13] showed that most neonates born to SARS-CoV-2-positive mothers are negative at birth

and that more than half of the positive infants were asymptomatic. It is known that pregnant women are prone to more severe respiratory infections with a higher mortality. During pregnancy, the upper respiratory tract tends to be swollen by a high level of estrogen and progesterone, increasing susceptibility to respiratory pathogens [14]. Maternal immunological state changes with the growth of the fetus, from a pro-inflammatory state in the first trimester to an anti-inflammatory state in the second trimester to a second pro-inflammatory state in the third trimester, in preparation for delivery [15]. So, the cytokine storm induced by SARS-CoV-2 may cause more severe inflammatory state.

In our study, most of the positive women were asymptomatic or paucisymptomatic without serious complications. Our results are consistent with a recent systematic review in which maternal fever has been reported as the most frequent prenatal sign, followed by cough and nausea [10].

Maternal SARS-CoV-2 infection has been associated with increased rate of C-sections and higher risk of pre-term labor [16]. A higher rate of C-section was found in Bari, but this difference reflects a different approach, not SARS-CoV-2 related, between North and South of Italy [17]. Regarding prematurity, the incidence of preterm newborns (11%) is consistent with the 6% reported by a recent systematic review, although a pathogenetic role of SARS-CoV-2 infection remains debatable [18].

Breastfeeding and rooming-in recommendations differ among different International Health Organizations [19–21]. According to the Italian National Institute of Health (ISS), the Italian Society of Neonatology (SIN), and the Union of European Neonatal and Perinatal Societies (UENPS), asymptomatic women should breastfeed with a surgical mask and careful hand hygiene. Based on the current knowledge, infection by breast milk has not been reported, as for other respiratory viral infections, and many studies showed negative RT-PCR for SARS-CoV-2 in breast milk samples from positive mothers [7].

Rooming-in, if possible, is also suggested, after maternal informed consent, to promote breastfeeding and mother-child relationship. The local epidemiological or logistic situation may reduce this possibility, as demonstrated by data from Bari (48% vs. 89% in Varese). The high rate of rooming-in in Varese is a good explanation for the higher breastfeeding rate at discharge (93% vs. 48% in Bari). This difference disappeared at 1 month of life when >75% of newborns were breastfed both in Bari and in Varese groups. It is possible that the early dis-

charge has a beneficial impact promoting mother-child relationship and, consequently, breastfeeding.

At home, breastfeeding can be started or continued, according to maternal clinical conditions and willing [7], being a safe practice, as shown by the very low rate of positive newborns at 1 month of age. Moreover, all neonates remained asymptomatic, confirming that breast milk does not increase the risk of SARS-CoV-2 infection.

As a general rule, breastfeeding is the normative standard of infant nutrition, representing the most complete and safe form of nutrition for neonates and infants. In particular, breast milk, with its anti-infective and anti-inflammatory factors, is crucial in reducing the risk of infections [22], as demonstrated for influenza in which breast milk may provide antibodies against this specific infection [23]. Regarding safety of breastfeeding of SARS-CoV-2-positive mothers, available data to date show rare mother-infant transmission [22].

Maternal-infant transmission of infection and its effects on neonatal and infant outcomes represent a significant medical issue. A recent Italian report showed 2 cases of perinatal transmission, but both infants were asymptomatic/paucisymptomatic, and breast milk of both mothers was negative [24]. In our experience, we follow the WHO guidelines that does not suggest separation of infants from their mothers and recommend skin to skin, rooming-in, and encourage breastfeeding [25], considering that the well-known benefits of breastfeeding overcome the very small risk of SARS-CoV-2 transmission, and also COVID-19 in infants is rare and generally not very severe [4].

Our data are consistent with other recent studies, suggesting that following protective measures, postnatal transmission is unlikely [26]. The most recent AAP neonatal guidelines [27] recommend rooming-in unless mothers are too ill to care for their newborn and confirm the importance of preventive measures to reduce SARS-CoV-2 infection.

Although we are aware of the several limitations, including no blood, milk, urine, or stool test, our study showed perinatal and postnatal SARS-CoV-2 transmission is unlikely and rooming-in and breastfeeding are safe, with infection control measures. Another bias of our study is the significant high number of non-re-tested infants in Bari with only 5 (5.5%) due to quarantine.

Conclusion

Our findings confirm that separation of affected mothers and newborns may not be warranted, and breastfeeding should be encouraged since it does not increase the risk of COVID-19. Understanding the impact of SARS-CoV-2 infection in pregnancy and maternal and neonatal outcome is needed for prevention and infection control.

To date, vertical and perinatal transmission is rare, and after discharge, postnatal transmission can be avoided if preventive measures are carefully followed. Larger studies can confirm our data, and a long-term follow-up for all newborns to SARS-CoV-2-infected mothers is mandatory.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The Ethics Committee of Sette Laghi Hospital of Varese, Italy, approved the study (No. 46322; April 7, 2020). The Ethics Committee of A.O.U.C. Policlinico of Bari, Italy, received the approval of the Ethics Committee of Varese. Informed consent was signed by all participant mothers.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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The authors declare no funding sources and no sponsor in the study.

Author Contributions

M.C. conceptualized and designed the study, drafted the initial manuscript, and revised the manuscript; S.I., R.P., S.P., and L.M. led the data acquisition and interpretation; A.V. and M.F. made statistical analysis and revised the manuscript; N.L., M.B., M.C., S.S., and M.A. made substantial contributions to the conception of the study, interpretation of the data, and reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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