Diagnostic challenges, management, and outcome of infants born to mothers with COVID 19 during the first wave of the pandemic

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Abstract. Severe acute respiratory distress syndrome with coronavirus 2 (SARS-CoV-2) infection affected pregnant women during the pandemic. Immunological particularity of this population and the increased need for medical assistance placed this population in a high-risk category for SARS-Cov-2 infection. Owing to high contamination risk and limited studies regarding vertical transmission, the labor and delivery of positive women required particular conditions. Cesarean section probably proved to be the optimal option for delivery of infants to reduce the risk of infection during birth. The aim of the present study was to present the management and outcome of infants born to mothers confirmed with coronavirus disease 2019 (COVID 19) prior to delivery. This is a longitudinal, retrospective study, analyzing demographics, laboratory data and management of neonates born to mothers with diagnosis of SARS-Cov-2 infection. The results showed that 5 neonates were born to SARS-Cov-2-positive mothers, all by Cesarean section and had a negative reverse transcription-quantitative polymerase chain reaction (RT-qPCR) test. None of the women breastfed during the hospital stay. The negative RT-qPCR test allowed us to reduce the hospital stay of infants and care in non-isolated areas. In summary, in the present study, vertical or perinatal transmission of the infection was not present. The testing of the pregnant women, their isolation and delivery in safe conditions for the medical staff were possible, with the latter using adequate protection equipment to limit their infection and the risk for the newborns.

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Abbreviations: SARS-CoV-2, severe acute respiratory distress syndrome with coronavirus 2; COVID 19, coronavirus disease 2019; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; CBC, central blood count; PPE, personal protection equipment; ARDS, acute respiratory distress syndrome; WBCs, white blood cells; IgM, immunoglobulin M; IgG, immunoglobulin G

Key words: COVID 19, neonate, pregnant women, transmission of infection, breastfeeding

Introduction

SARS-CoV-2 infection can determine various forms of respiratory insufficiency (ARDS) with clinical and radiological features of pneumonia (1). Similarly, the SARS-Cov2 infection has also affected the population of pregnant women during the pandemic. At present, the predominant symptoms, the rate of morbidity and mortality among pregnant women are not known.

The immunological particularity of this population is represented by its high susceptibility to infections due to hormonal changes during pregnancy. It is well accepted that, due to the increased need for medical assistance and pregnancy monitoring, this population presents a high contamination risk. There are few data regarding the incidence of pneumonia caused by SARS-CoV-2 in the period of pregnancy. The majority of pregnant women who contracted the infection were asymptomatic or presented mild symptoms (2-5).

The vertical transmission of the infection to the newborn, even in the case when the mother is symptomatic, has been described in a few cases (1,6). The risk of contamination of the newborn seems higher in the immediate postnatal period, from the infected symptomatic or healthy carrier mother, if strict hygienic measures are not respected during skin-to-skin care. Due to COVID 19 high contagion, obstetricians, neonatologists and infectious disease specialist have focused on the implementation of preventive measures in all areas (from the delivery room, to the neonatal, maternity ward and intensive care unit) to limit the risk of viral transmission (3,7-9).

Breastfeeding in the immediate postpartum period remains a problem in certain situations. Although breastfeeding is recommended, this is not always possible, since the mother may require isolation and treatment in a different hospital service than that in which delivery occurs. This limits the breastfeeding of the newborn, with the loss of the important benefits of this type of feeding, including the protective benefit against infections (3,10).

The aim of the present study was to present the management and outcome of infants born to mothers confirmed with coronavirus disease 2019 (COVID 19) prior to delivery. Although the infants had a negative result, breastfeeding did not occur during hospital stay.

Patients and methods

Patient characteristics. Between April 1st and May 15th, 2020, 229 pregnant women with an age range of 18-47 years, and a mean age of 30.22 years, were admitted for delivery in the Clinic of Obstetrics and Gynecology Ist, County Emergency Hospital, Cluj-Napoca, Romania, a tertiary level hospital. Among them, five tested positive for SARS-Cov-2 infection. The newborns were admitted to the Neonatology Department of the Clinic of Obstetrics and Gynecology Ist.

Institutional review board and research committee approval of County Clinical Emergency Hospital, Cluj Napoca, Romania, was obtained for the present study, under no. 27150/01.09.2020. All charts of newborns from SARS-Cov-2-positive women were retrospectively reviewed. Written informed consent was obtained from the newborns' parents.

Parameter. All neonates of mothers with SARS-CoV-2 infection, were delivered by Cesarean section, in the designated operating room for cases with SARS-CoV-2 infection. After delivery, the newborns were admitted to the quarantine ward according to the local protocol. An umbilical venous catheter was placed, and prophylactic antibiotic therapy was administered. Vital functions including temperature, respiratory rate, heart rate, blood pressure, and oxygen saturation were assessed. Laboratory parameters were monitored including, central blood count (CBC), and the inflammatory markers, C-reactive protein (CRP) and procalcitonin, glycemia, creatine kinase, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase. The CBC was evaluated on the first day of life while all the other parameters were measured on the 1st and 3rd day of life.

Testing. All the newborns underwent SARS-CoV-2 testing using the reverse transcription-quantitative PCR (RT-qPCR) technique from the upper airway specimens (nasopharyngeal and pharyngeal swabs). The testing was carried out on the first day and fifth day of life. Sampling was performed by a physician wearing appropriate personal protection equipment (PPE), in the quarantine room. Each nasopharyngeal swab was collected in the Nasopharyngeal Sample Collection Kit for Viruses (Dakewe Bio-engineering Co., Ltd.) and transferred to the laboratory. Within the negative-pressure fume hood 30 ml of viral culture media from the collection kit were extracted. Nucleic acid isolation was performed with a STARlet IVD Microlab (Hamilton), automat extractor. A cartridge was placed in the Biorad CFX96 equipment (Bio-Rad Laboratories, Inc.) for polymerase chain reaction, via RT-qPCR. The result was scored as 'positive' or 'negative'. Data were collected from the infant's charts and centralized in tables. Results are presented as absolute frequency.

Results

Maternal cohort. Between April 1st and May 15th, 2020, 229 pregnant women were admitted for delivery. All 229 women were tested for COVID 19 infection, using throat swab specimens and infection was confirmed by RT-qPCR. Five (2.18%) of these 229 patients had a positive RT-qPCR test: four of them were diagnosed COVID 19 positive (+) at the time of admission for delivery, while one patient was transferred for delivery from the infectious diseases department after a hospitalization period of 20 days; at the time of the transfer, she presented a positive RT-qPCR test.

Three of the five COVID 19+ women were asymptomatic at the time of admission. One of them presented with gestational diabetes; a risk factor for severe form of infection. None of the five enrolled women had come into contact with a SARS-CoV-2-positive person or had travelled to an affected area. Another woman presented symptoms of acute respiratory infection (fever, sore throat and cough) one week prior to delivery; she received symptomatic treatment (paracetamol) and vitamin C.

All positive mothers underwent Cesarean section. These mothers were admitted postoperatively to separate wards, maternal quarantine wards, and were transferred to the Department of Infectious Disease 72 h later.

Demographic and general characteristics of infants. Of the 229 deliveries, 108 were by vaginal route and 121 by Cesarean section. There were 186 neonates at term, and 43 preterm neonates. The demographic characteristics and the general data of the newborns born to the 5 COVID 19+ mothers are shown in Table I.

One newborn born to a COVID 19+ mother was preterm. The pregnant woman was admitted for minimal hemorrhage, and the test for SARS-CoV-2 at admission was positive. Delivery by Cesarean section was decided.

Laboratory data. In all the newborns of the studied group, the evolution of CBC, of inflammatory markers CRP and procalcitonin were dynamically monitored, on the first and third day of life. The variation of the monitored laboratory parameters is shown in Table II.

In four newborns, white blood cells (WBCs) and platelets were within the normal range. In one of five newborns (patient 1), inflammatory markers were reacted on the first day of life (CRP=1.27 mg% and PCT=20.13 ng/ml), and neutrophilia with mild lymphopenia was present (Table II). The infant received antibiotic therapy for 7 days, with laboratory tests returning to normal values. There were no clinical symptoms suggestive of neonatal sepsis. This patient had a symptomatic mother one week before delivery. The mother's therapeutic response was slow and the first SARS-CoV-2-negative test was obtained 5 weeks after delivery.

Management. All newborns had an umbilical venous catheter inserted immediately after delivery. The umbilical venous catheter was maintained until the second negative RT-qPCR was obtained. For all the newborns, the RT-qPCR tests performed on the first day and on the 5th day of life were negative.

Table I. Demographic and general characteristics of the infants born to the 5 COVID 19-positive mothers.

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gestational age (weeks)	38	39	36	38	38
Birth weight (g)	3,370	3,210	2,350	3,070	3,200
Length (cm)	53	52	50	53	53
Head circumference (cm)	34	33	32	34	34
Apgar score (1' and 5')	10/10	10/10	9/9	10/10	10/10
Gender (M, male/F, female)	F	F	F	M	F
Gravida (parity)	II	III	I	I	I

Enteral feeding with formula was administered. Feeding with breast milk during admission to the maternity ward was not possible for any of the newborns with SARS-CoV-2-positive mothers. They received breast milk only after the mother's discharge from the infectious disease service. All neonates were exclusively breastfed in the first 6 months after birth.

No patient required oxygen supplement or respiratory support. There were no complications during hospital stay for any of the patients.

The mean length of hospital stay was 12.2 days (6-22 days). The longest hospital stay was determined by the long hospital stay of the mother, until the mothers obtained a negative SARS-CoV-2 test.

The hospitalization period of the newborn was marked by no pathological event. The follow-up of infants suggested normal evolution in the first 10 months of life without any infectious disease during this period of life.

Discussion

The presence of SARS-CoV-2 infection in pregnant woman involves risks for the newborn. No case of vertical transmission was reported in our unit during the mentioned period. To prevent perinatal transmission and contamination of the medical staff, in the period of onset of the pandemic, the national guidelines for obstetrics and neonatology recommended delivery by Cesarean section in pregnant women positive for SARS-CoV-2, as well as for pregnant women suspected to be infected (those with travel history, contact with SARS-Cov-2-positive persons or presenting respiratory symptoms) (2,3,10,11).

The exact rate of vertical transmission of the infection is not known. Currently, only a limited number of cases with vertical transmission are reported. Seven independent studies reported the outcomes of 70 newborns of mothers with confirmed SARS-CoV-2 infection: 65 neonates (92.9% of cases) were negative following RT-qPCR analysis of oropharyngeal or nasopharyngeal swab performed in the first hours or days of life; in four patients (5.7% of cases), early infection was diagnosed on the second day of life; thus, vertical transmission cannot be excluded; finally, one patient had a negative throat swab but positive immunoglobulin M (IgM) and immunoglobulin G (IgG) count, and was considered as potentially infected *in utero*. Consequently, in 5 out of 70 cases (7.1% of neonates), vertical transmission could not be excluded or was considered possible (4,12-17).

In our group, all five neonates of SARS-CoV-2-positive mothers were born by Cesarean section. In the majority of the reported cases, the delivery of the newborns of mothers with SARS-CoV-2 infection was performed by Cesarean section. The aim of this mode of delivery is to limit the perinatal transmission of the infection from the mother to the neonate, as well as to limit the contamination of the medical staff by assisting the infected pregnant woman during labor and expulsion, which can last a considerable period of time (18).

The neonates of our study group had a favorable clinical outcome, without events during hospitalization. No changes in the values of lymphocytes, neutrophils or leukocytes were reported. Inflammatory syndrome was negative, except for patient 1, which had CRP and PCT beyond of normal range (Table II). Early inflammatory syndrome present in one neonate had a favorable evolution following antibiotic treatment. This patient had no clinical elements suggestive of neonatal sepsis and had negative blood culture. One week before delivery, the mother had symptoms suggestive of SARS-CoV-2 infection (fever, cough, sore throat). There were no other maternal risk factors explaining inflammatory syndrome in the newborns. No analysis of the placenta was performed in this period because of the high infection risk. The creatine kinase (CK) value was beyond the normal range in three patients on the first day of life, but the third day value was within the normal range (Table II). The aspartate aminotransferase and lactate dehydrogenase had the same behavior in two of the patients; however, no explanations can be provided for this finding (Table II). It is known that SARS-Cov-2 infection is associated with liver function abnormalities. Nevertheless, this type of abnormal laboratory data was not anticipated for the infants owing to their negative RT-qPCR tests.

The analysis of the oropharyngeal or nasopharyngeal swab was negative in all newborns of the study group, on the first as well as on the fifth day of life. Umbilical vein catheterization was carried out in all the patients to facilitate collection of the laboratory tests, to limit the length of time spent for blood sample collection and to allow a safe venous approach for eventual medication. After obtaining the second negative test, the venous catheter was removed from all the patients.

Enteral nutrition was given in accordance to the local national guidelines. In all neonates with RT-qPCR-positive mothers, enteral nutrition was initiated with formula. Although there were tests showing that the breast milk of women with SARS-CoV-2 infection was negative, formula was given to the neonates (3,19). The mothers were placed in a designated area

Table II. Evolution of laboratory parameters.

Parameter	Day of life	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
HGB (g/dl)	1	18.4	14	14.9	18.4	15.70
HCT (%)		51.8	39.8	43.6	52.2	44.40
PLT (10^9/l)		369	318	268	159	291
WBCs (10^9/l)		26.50	26.94	21.57	7.45	26.20
Ne (%/10^9/l)		70.9/18.8	69.3%/18.65	69.2%/14.94	45%/3.35	60.9%/15.96
Ly (%/10^9/l)		21.1%/5.6	21.8%/5.86	24.4%/5.27	37.1%/2.77	31.7%/8.3
ASAT	1	49	**117**	**93**	55	47
(NV 25-75 U/l)	3	34	29	65	51	44
ALAT	1	29	22	13	21	12
(NV 13-45 U/l)	3	32	20	20	24	14
CK	1	**848**	**1,225**	**1,316**	525	NA
(NV <712 U/l)	3	306	204	303	468	NA
LDH	1	529	**904**	**790**	467	NA
(NV 290-775 U/l)	3	49	117	93	55	47
C-reactive protein	1	**1.27**	0.14	0.17	0.12	0.1
(CRP) (mg%)	3	0.46	0.06	0.24	0.10	0.18
(NV<0.5 mg%)						
PCT (ng/ml)	1	**20.13**	NA	NA	NA	1.96
(NV<0.2 ng/ml)	3	4.39	NA	NA	NA	0.4

NV, normal value; NA, not available; bold, beyond normal value. HGB, hemoglobin; HCT, hematocrit; PLT, platelets; WBCs, white blood cells; Ne, neutrophils (% and absolute no.); Ly, lymphocytes; PCT, procalcitonin; ASAT, aspartate amino transferase; ALAT, alanine amino transferase; LDH, lactate dehydrogenase; CK, creatine kinase.

of the maternity wards for the first 72 h after the Cesarean section, after which they were transferred to the contagious disease unit.

Feeding with breast milk has a number of benefits for both the mother and the newborn, the immunological benefit playing an important role in the protection of the newborn from infections through the transfer of immunoglobulin with a protective role for the neonate. The recommendation for breastfeeding in the case of mothers infected with SARS-CoV-2 is to maintain rigorous hygiene conditions, to wash and disinfect hands, and to wear a mask during breastfeeding. If the mother cannot breastfeed the newborn, expressed breast milk can be used, while respecting the same rigorous hygiene conditions for expressing breast milk. If the mother is separated from the neonate, it is recommended to help the mother maintain lactation by manual or mechanical expression. In addition, counseling of the mother and the family in case of separation from the newborn should be taken into consideration, and permanent communication with the family and information regarding the health of the neonate should be ensured (20,21). Whenever possible, feeding the neonate with breast milk is recommended if the mother's condition allows it and if she wishes to breastfeed under the current health conditions (2,9,13,21).

The strengths of this study include the timely nature of our findings as the COVID 19 pandemic ensues, and the evaluation of the incidence of infection among the pregnant women in our region. The weakness of the present study is the relatively small size of the group, albeit the evidenced data are in accordance with those obtained by similar studies. These data are useful for the analysis of the obstetric population, as well as for knowledge of the risk of infection in this population. Testing all pregnant women at admission to the maternity unit is an important method to reduce the spread of SARS-CoV-2 infection, representing a guide in the approach of delivery in pandemic conditions.

In summary, in the present study, vertical or perinatal transmission of the infection was not present in any of the neonates. As in the majority of the cases from other studies, the newborns included in the present study were negative on RT-qPCR testing via nasopharyngeal swab. Testing confirmed the absence of infection and allowed the transfer of the neonates to the non-isolated area. Thus, the hospital stay of the neonates was limited, their discharge to the family being possible when the family members were healthy, and no longer in quarantine.

The diagnosis of SARS-CoV-2 infection of the pregnant women was established at admission to the maternity ward. Due this testing, the mother's isolation and delivery in safe conditions for the medical staff were possible, using adequate protection equipment to limit infection and to limit any risk for the newborns.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

GZ contributed to the conceptualization and methodology, confirmed the authenticity of the raw data and was involved in the writing of the manuscript. MM performed the data collection, confirmed the authenticity of the raw data, and was involved in the writing of the manuscript and literature research. MH interpreted the results and carried out the data analysis. TK contributed to the study design and acquisition of data. DM contributed to the revision of the manuscript and data interpretation. All authors read and approved the submitted version of the manuscript.

Ethics approval and consent to participate

Institutional review board and research committee approval (no. 27150/01.09.2020) from the County Clinical Emergency Hospital, Cluj Napoca, Romania, was obtained. Informed consent for the study was obtained from each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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