Case Series

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TANAFFOS

COVID-19 Infection in Iranian Newborns and their Mothers: a Case Series

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Background: The symptoms, severity, and prognosis of coronavirus disease 2019 (COVID-19) are surprisingly different in neonates versus adults or even children. Currently, there are few studies on neonatal and maternal COVID-19 with limited populations.

Case Presentation: In this study, we present 13 Iranian symptomatic newborns with a positive nasopharyngeal COVID-19 test and their maternal data on COVID-19. All neonates were admitted to the hospital at the first day of life, mostly having symptoms at birth, except three cases that had symptoms at days 2, 11, and 22. Almost all cases had respiratory distress and were tachypneic, which needed respiratory support. Although most cases were discharged after recovery, two patients died at days 12 and 48.

Conclusion: Neonatal COVID-19 cases mostly had respiratory symptoms and subsequent radiographic features of a viral pneumonia; thus, they had an effective response to oxygen therapy. The symptoms were by far less severe in newborns, although we lost two cases to this infection. This highlights the necessity for good COVID-19 prognosis in infants and neonates.

Key words: COVID-19, Neonates, Newborns, Maternal

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is by all means the global health crisis of our time. The name of this new virus was announced severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on 11 February 2020 (1) because of being genetically related to SARS, responsible for 2003 outbreak, which had been implicated in maternal and neonatal morbidity and mortality at the time (2). Although all age ranges are susceptible to COVID-19, there is a gap in research in the neonatal field. The incidence rate of infection is relatively low in below 18 years of age (24% of all reported cases) (3) or even less in neonates, but the potential harm of COVID-19 remains largely unknown in this population. COVID-19 manifests different symptoms with less severity and hospitalization and death rate in children. The proportion of severe and critical cases of COVID-19 in pediatric cases in China was 10.6%, 7.3%, 4.2%, 4.1%, and 3.0% for the age group of <1, 1-5, 6-10, 11-15, and ≥16 years, respectively, suggesting a higher risk in neonates (4).

Moreover, there is a need for maternal study in newborns with COVID-19 not only due to the low risk of intrauterine infection by vertical transmission of SARS-CoV-2 (5), but also because of growing concerns regarding the effects of COVID-19 on pregnancy and parturition. Besides, the physiological changes in pregnant women make them more susceptible to pulmonary infections with poor prognosis (6).

Finally, due to the limited knowledge about maternal and neonatal COVID-19, clinicians are predisposed to

make uninformed and risky decisions. Thus, in this study we reported 13 cases of newborns with COVID-19 and their maternal data.

MATERIALS AND METHODS

Study Population

This multicenter research was conducted in four hospitals of three different cities in Iran including Hazrat-e Rasool General Hospital in Tehran, Khorami and Izadi hospitals in Qom, and Imam Reza hospital in Lar. Data were collected from the beginning of the declared COVID-19 pandemic in Iran in March 2020 to June 2020.

We presented 13 Iranian newborns. All symptomatic neonates had a positive result for COVID-19 according to nasopharyngeal reverse transcription polymerase chain reaction (RT-PCR) test. Also, we collected the maternal data of all cases. The COVID-19 PCR test was done twice for each case (with 48 hours interval time). To present only the confirmed cases, we excluded those symptomatic ones with negative COVID-19 PCR results.

Procedure

Medical records of all hospitalized neonates due to COVID-19 including, demographic information, clinical features of the disease, signs, symptoms, duration, blood tests, along with radiographic data (chest x-ray and spiral chest CT scan without contrast to review pulmonary infection) were collected. Also, brain sonography and echocardiography data were presented if available to detect other underlying abnormalities. Following the patients' progress, the outcome was also recorded.

We retrospectively collected maternal data of COVID-19 confirmed newborns, including age, underlying medical conditions, blood group, symptoms, and laboratory and radiographic data (if available). Besides, parturition-related data were collected and the patients' outcomes were presented.

CASE PRESENTATIONS

Neonatal Data

Tables 1-4 present 13 newborns (five females vs. eight males) with confirmed COVID-19 according to positive RT-PCR. All cases had two nasopharyngeal samples (with 48 hours interval time), except for two tracheal samples (cases 11 and 12). All neonates were admitted to the hospital at the first day of life, mostly having symptoms at birth except three cases that had symptoms at days 2, 11, and 22. Considering gestational age of below 37 weeks, nine cases were preterm. Also, considering 2500 g as the threshold, five neonates had a low birth weight. The most common delivery method was cesarean section (C/S), except for cases 1 and 6 that had normal vaginal delivery (NVD). Case 8 was the second child of a twin pregnancy; the first neonate had no symptoms. Apgar score was mostly normal except for two patients with scores 2 and 3. Also, four newborns needed cardiopulmonary resuscitation (CPR) at the birth time (cases 2, 8, 10, and 12).

The most common COVID-19 symptom was respiratory distress, for which we used Downe score to address the severity (7). Four newborns were lethargic. Cough and intolerance to feeding were recorded separately in two patients. One neonate had fever. None of them had tachycardia, although all were tachypneic needing respiratory support, including nasal O_2, continuous positive airway pressure (CPAP), or mechanical ventilator with duration from the range of 1 to 10 days (mostly 1 to 3 days).

Laboratory data showed that white blood cell (WBC) ranges were mostly normal among all cases, except one case of leukocytosis and one with leukopenia; both cases survived. Hemoglobin (Hb), hematocrit (HCT) and platelet levels were normal in all cases. Almost all cases had high C-reactive protein (CRP) levels, except five cases. Eight newborns had high lactate dehydrogenase (LDH) level and four had increased creatine phosphokinase (CPK) amounts. Liver aminotransferases were mostly normal (8).

Chest X-rays (CXR) demonstrated a wide range of findings from bilateral pulmonary infiltrations and ground glass opacities (GGOs) to air bronchogram pattern or even emphysema and white lung in one case that luckily survived later. Also, one patient had normal CXR and chest computed tomography (CT) scan.

Table 1. Neonates data, including admission date, gender, gestational age and the age of symptoms presentation, birth weight and apgar score

General data Newborn number	Admission at age (days)	Sex	Gestational age (weeks)	Age at the time of symptom onset (days)	Birth weight (Kilograms)	Apgar score (At 1 minute, at 5 minutes)
1	2	Female	39	2	3.4	4,8
2	1	Female	26	At birth	0.7	4,8
3	1	Male	34	At birth	2.5	7,8
4	1	Male	38	1	4.3	9,10
5	1	Female	39	At birth	3.1	8,9
6	1	Male	34	At birth	2.5	8,9
7	22	Male	36	22	3.4	-
8	1	Female	29	At birth	1.5	3,7
9	11	Male	39	10	3.5	9,10
10	1	Female	33	An hour after birth	1.9	7,9
11	1	Male	36	At birth	3.45	9,10
12	1	Male	34	At birth	0.7	2,5
13	1	Male	34	At birth	2.1	9,13

Table 2. COVID-19 neonates sign and symptoms and types of respiratory supports, including CPAP (Continuous positive airway pressure) and patient´s outcome

Newborn Number	1	2	3	4	5	6	7	8	9	10	11	12	13
Sign and symptoms													
Cough	+	-	-	-	-	-	-	-	-	-	-	-	-
Fever	-	-	-	-	-	-	-	-	+	-	-	-	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-
Intolerance to feeding	-	-	-	-	-	-	-	-	+	-	-	-	-
Lethargy	+	+	-	-	-	-	-	-	+	-	-	+	-
Agitation	-	-	-	-	-	-	-	-	-	-		-	-
Skin rash	-	-	-	-	-	-	-	-	-	-	-	-	-
Respiratiry distress	+	+	+	+	+	+	+	+	-	+	+	+	+
Vital signs at the time of admission													
Heart rate	130	138	148	154	153	158	-	140	160	155	135	145	125
Respiratory rate	110	110	44	60	68	78	-	67	36	70	110	60	60
Axillary temperature	36.8	36.8	37	36.2	36	36.1	-	36.2	37.8	36.6	37	36	36
RDS score	5	7	-	-	-	-	-	7	0	8	10	9	8
Retraction	-	+	+	+	-	+	-	+	-	+	+	+	+
Cyanosis	+	+	-	+	-	+	+	+	-	+	+	+	+
Grunting	+	+	+	+	-	+	-	+	-	+	+	-	+
Types of respiratory support													
Respiratory support by nasal O2 (days)	-		-	-	-	-	+	1	+	2	1	-	2
Respiratory support by CPAP ventilation (days)	+	+	+	+	2	-	-	2	-	2	1	-	2
Respiratory support by mechanical ventilation (days)	-	-	-	-	-	+	-	3	-	1	1	10	-
Patient´s outcome													
Discharge after recovery (hospitalized days)	9	26	9	5	+	7	-	17	7	15	20	-	8
Quarantine at home	-	-	-	-	-	-	-	-	-	-	-	-	-
Age at the time of death (days)	-	-	-	-	-	-	47	-	-	-	-	12	-

The normal range for vital signs are as follows: heart rate (120-160 beats per minute), respiratory rate (30-60 breaths per minute) and axillary temperature (36.5-37.4 ºC). Rectal temperature is not checked in neonates due to the possibility of rectal damage. Respiratory distress syndrome (RDS) severity according to Downe score indicates: 0: no respiratory distress, 1-4: mild, 5-7: moderate and 8-10 severe respiratory distress.

Table 3. Neonatal laboratory data.

Newborn Number / Laboratory data	1	2	3	4	5	6	7	8	9	10	11	12	13
WBC (102 per microliter)	182	127	48	230	130	180	135	220	120	210	367	218	228
Neutrophil percentage	80	40	43	60	40	60	45	68	65	80	80	20	77
Lymphocyte percentage	20	60	33	38	60	39	50	26	30	19	20	78	13
Hb (grams per deciliter)	21.1	14.7	18.1	16	16	16	15	16	16	14	16.2	17.7	16.7
HCT percentage	58	41.8	50	-	-	-	-	49	50	42	46	53	52
Platelet (103 per microliter)	148	296	174	220	182	149	242	238	256	180	253	164	184
CRP (milligrams per liter)	3+	Neg.	Neg.	19	18	6	5.5	12	14	6	39	56	48
Ferritin (micrograms per liter)	-	-	-	-	-	-	-	300	700	20	-	-	-
LDH (units per liter)	752	667	463	600	-	348	601	780	1400	140	3140	-	1600
CPK (micrograms per liter)	600	169	450	500	-	242	300	1178	7800	180	1047	-	1200
AST (international units per liter)	62	18	42	13	-	13	22	42	32	18	119	-	-
ALT (international units per liter)	13	22	13	19	-	19	14	30	22	22	39	-	-
BUN (milligrams per deciliter)	22	6	7	10	5	15	9	11	12	18	16	13	13
Cr (milligrams per deciliter)	1.1	0.7	0.5	0.7	0.6	0.9	0.3	0.8	0.4	1	0.5	1	1
Albumin (grams per deciliter)	3	3	-	-	-	-	-	2.5	3.2	4.5	-	-	3

Neonatal laboratory data are presented as follows: WBC: White blood cell, Hb: Hemoglobin, HCT: Hematocrit, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, LDH: Lactate dehydrogenase, CPK: Creatine phosphokinase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, Cr: Creatinine.

Table 4. Neonatal imaging data, including chest X-ray and spiral chest CT scan without contrast and also Brain sonography and even echocardiography

Imaging data / Newborn number	Chest X-Ray	Chest CT scan	Brain Sonography	Echocardiography
1	Bilateral infiltrations	-	Normal	Mild TR
2	Reticulonodular, GGOs	-	Normal	Small PDA
3	Normal	-	Normal	Normal
4	Emphysema	-	-	-
5	GGOs	-	Normal	Large PDA
6	GGOs, hypoinflation	-	Normal	Mild TR
7	Bilateral infiltrations	Diffuse GGOs	-	PHTN, moderate TR
8	RDS, infiltration	-	Normal	Normal
9	Mild infiltration	-	-	-
10	Airbronchogram	-	Normal	Normal
11	White lung	-	-	Mild TR, PFO, mild PHTN
12	Diffuse patchy infiltrations	Diffuse GGOs	-	-
13	Airbronchogram	-	Normal	Normal

Abbreviations are as follows: TR: Tricuspid regurgitation, GGO: Ground glass opacities, PDA: Patent Ductus arteriosus, PFO: Patent foramen Oval, PHTN: Pulmonary hypertension, RDS: Respiratory Distress Syndrome.

All cases had normal brain sonography. Echocardiography was performed for most patients with no serious heart problem.

According to the outcomes, most of the patients were discharged after an average of 12 days of hospitalization. Discharge criteria included asymptomatic with good general condition, normal passage of urine and stool, tolerance to oral feeding, and rule out of bacterial infection. Unfortunately, we lost two patients; one had respiratory distress and Apgar scores of 2 and 5 at minutes 1 and 5 after birth, respectively, that went through a successful CPR but died at day 12. The other one had symptoms at day 22 while weighing 4.3 kilograms. Unfortunately, he also died at day 47.

Maternal data

Tables 5-9 represent maternal data of our COVID-19 confirmed newborns. Seven, out of 13 mothers, were asymptomatic, all with negative RT-PCR for COVID-19

with no other medical records. In retrospective investigations about neonates with asymptomatic mothers, three cases had close contact with neonatal intensive care unit (NICU) nurses of Lar city hospital, that proved to be silent carriers for COVID-19 confirmed by PCR; and the father of one of the newborns had a positive COVID-19 result (cases 1, 2, 3, 4, and 9). Fever, cough, dyspnea, and myalgia were some of the mothers' symptoms. Among symptomatic mothers, three had positive PCR results for COVID-19 and two had radiographic data in favor of pulmonary infection. Four mothers were hospitalized and recovered after a few days and none of them were admitted to the ICU. Also, we presented the available laboratory data; two leukocytosis, three lymphopenia, and three cases of increased CRP levels were detected.

Other outcomes of interest were age range of 22-40 years, past medical history (presented in Table 5), and blood group (six O+, four A+, two B+, and one AB+).

The pregnancy measures of interest presented in Table 9 were duration of symptoms before parturition, which varied from asymptomatic or 2 to 20 days before delivery, rupture of membrane (ROM) (in 3 cases) to parturition duration from 2 to 24 hours and clear or meconium-stained amniotic fluid.

Table 5. Maternal general data, including age, medical conditions and blood group

General data Mother number	Age (years)	Underlying disease	Blood group
1	30	-	O+
2	22	-	O+
3	33	DM(insulin)	O+
4	29	-	O+
5	25	GDM	B+
6	31	Hypothyroidism, thalassemia minor	A+
7	35	DM	AB+
8	32	-	O+
9	31	-	B+
10	26	-	A+
11	40	Hypothyroidism	O+
12	39	HTN	A+
13	25	DM	A+

Maternal underlying disease abbreviations are as follows: DM: Diabetes mellitus, GDM: Gestational DM, HTN: Hypertension.

Table 6. Maternal symptoms of COVID-19 infection if exist and the patients outcome

Mother Number	1	2	3	4	5	6	7	8	9	10	11	12	13
Symptoms													
Fever	-	-	-	-	-	+	-	+	-	+	-	+	+
Cough	-	-	-	-	-	+	-	-	-	+	+	-	+
Dyspnea	-	-	-	-	-	-	-	-	-	+	+	-	-
Sore throat	-	-	-	-	-	-	-	-	-	-	+	-	-
General weakness	-	-	-	-	-	-	-	-	-	-	-	-	-
Myalgia	-	-	-	-	-	+	-	-	-	-	-	-	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-
Headache	-	-	-	-	-	-	-	-	-	-	-	-	-
Lack of smell or taste	-	-	-	-	-	-	-	-	-	-	-	-	-
Patient´s outcome													
Discharge after recovery	-	-	-	-	-	+	-	+	-	+	+	-	-
Quarantine at home	-	-	-	-	-	-	-	-	-	-	-	+	+

Table 7. Maternal laboratory data if available.

Mother number / Laboratory data	1	2	3	4	5	6	7	8	9	10	11	12	13
WBC (102 per microliter)	-	-	-	-	-	120	-	72	60	100	76	124	114
Neutrophil percentage	-	-	-	-	-	-	-	40	30	55	79	76	80
Lymphocyte percentage	-	-	-	-	-	12	-	60	68	45	23	14	14
Hb (grams per deciliter)	-	-	-	-	-	12.6	-	14	14	13.5	11	8.2	11.2
HCT percentage	-	-	-	-	-	-	-	45	44	42	33	26.8	36.8
Platelet (103 per microliter)	-	-	-	-	-	180	-	230	180	260	410	-	280
ESR	-	-	-	-	-	30	-	12	14	28	-	-	24
CRP (milligrams per liter)	-	-	-	-	-	28	-	7	5	22	-	-	26
Ferritin	-	-	-	-	-	-	-	70	70	400	-	-	40
LDH (units per liter)	-	-	-	-	-	552	-	150	120	500	-	-	140
CPK (micrograms per liter)	-	-	-	-	-	600	-	120	100	600	-	-	160
AST (international units per liter)	-	-	-	-	-	13	-	22	20	-	-	26	27
ALT (international units per liter)	-	-	-	-	-	32	-	20	18	-	-	11	21
BUN (milligrams per deciliter)	-	-	-	-	-	15	-	18	12	14	11	7	7
Cr (milligrams per deciliter)	-	-	-	-	-	1	-	0.7	0.7	0.8	-	0.7	0.7
Albumin (grams per deciliter)	-	-	-	-	-	-	-	3.5	4	4	-	-	-

Maternal laboratory data are presented as follows: WBC: White blood cell, Hb: Hemoglobin, HCT: Hematocrit, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, LDH: Lactate dehydrogenase, CPK: Creatine phosphokinase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, Cr: Creatinine.

Table 8. Maternal Nasopharyngeal swab RT-PCR test results if available and also radiographic data

Mother Number	Nasopharyngeal swab RT-PCR first time	Nasopharyngeal swab RT-PCR second time	Chest X-Ray	Chest CT scan
1	Negative	Negative	-	-
2	negative	Negative	-	-
3	-	-	-	-
4	Negative	Negative	-	-
5	Negative	Negative	-	-
6	Negative	Negative	Normal	GGOs
7	Negative	Negative	-	-
8	Positive	Positive	Normal	-
9	Negative	Negative	Normal	-
10	Positive	Negative	Mild infiltration	-
11	Negative	-	-	-
12	Negative	-	-	-
13	Positive	Negative	-	-

Abbreviations are as follows: GGOs: Ground glass opacities.

Table 9. Maternal parturition related data

Mother Number / Parturition related-data	1	2	3	4	5	6	7	8	9	10	11	12	13
Symptoms duration before parturition (days)	-	-	-	-	-	-	-	10	-	16	19	2	20
ROM	-	-	-	-	+	+	-	-	-	+	-	-	-
ROM to parturition duration (hours)	-	-	-	-	16	24	-	-	-	2	-	-	-
Clear AF	-	-	+	-	+	+	-	+	+	+	+	+	+
Meconium-stained AF	+	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations are as follows: ROM: Rupture of membranes, AF: Amniotic fluid.

DISCUSSION

In this study, we presented 13 newborns with COVID-19 infection mostly admitted to the hospital at the first day of life, having symptoms at birth, except three cases that had symptoms at days 2, 11, and 22. The first COVID-19 infected newborn in the world was a 17-day-old boy, that recovered with symptomatic treatment (9). Also, a study on Chinese neonates (age: 30 hours to 17 days old) with mild symptoms showed that there was no need for mechanical ventilation and the patients recovered after receiving symptomatic treatments (10). However, another study indicated continuous positive airway pressure therapy as one of the common respiratory supports for COVID-19 in neonates (11).

Regarding gender, there were five females and eight males with almost similar disease severity and outcomes, including the hospitalization days. Almost all neonates recovered after a few days of receiving oxygen therapy, as the main treatment in the hospital. Unfortunately, two male newborns, third and first in the family, with gestational ages of 34 and 36 weeks, and birth weight of 0.7 and 3.4 kilograms, died at days 12 and 47, respectively. They had no significant congenital problems. Arguably, adult males are more likely to develop severe symptoms due to androgen sensitivity model (12), which seems to be irrelevant in children. Therefore, the gender mortality imbalance might be due to the unequal number of each gender in our study.

Tachypnea, fever, and cough were reported as the most common symptoms of COVID-19 in a case series of nine Iranian children in the age range of 2-10 years (13). Being tachypneic and having respiratory distress were recorded in almost all our neonates, but the latter symptoms were rare in our study. Respiratory distress was reported to occur only in Chinese children and neonates with underlying medical conditions, e.g., congenital heart and kidney problems (14); however, there was no record of congenital problems in the neonates of interest in our study.

Laboratory data including WBC, Hb, and platelet were mostly normal in our neonates. Almost all patients had high CRP levels, except five cases. Besides, high levels of LDH and CPK were detected in some cases. In accordance with our data, other studies have shown elevated CRP and LDH in most neonatal cases, along with increased liver enzymes. The WBC in COVID-19 neonates varies from normal to leukocytosis or even leukopenia (15). In our research, CXR findings of neonates demonstrated a wide range from normal to bilateral pulmonary infiltrations and ground glass opacities, air bronchogram pattern, or even emphysema, and also white lung in one case. Consistent with our study, in a research on newborns of 29 pregnant women with COVID-19 in Wuhan, China, five neonates had radiological features of viral pneumonia but a negative nucleic acid amplification test (16).

To investigate the perinatal consequences and vertical transmission, a study of 19 Chinese neonates born to mothers with COVID-19 was done which declared no symptoms or PCR and even radiologic findings in favor of COVID-19 (17). Another case series did not show detectable SARS-CoV-2 in amniotic fluid or the umbilical cord blood of pregnant COVID-19 symptomatic mothers, being monitored to the delivery of neonates with average gestational age of 38.6 weeks and average birth weight of 3293 g (18). However, in our study, six mothers were symptomatic. This might be due to the study type because our case was tracking down the maternal data of confirmed COVID-19 neonates retrospectively. Also, in our study population, nine neonates were preterm, five had low birth weight, and three mothers had rupture of membranes. In line with our data, a research on risks of COVID-19 in pregnancy reported six premature rupture of the membranes and six preterm labor in 37 mothers with COVID-19 (19).

This study had some limitations. All our patients were symptomatic neonates and there was no asymptomatic case in our research; however, PCR test under 24 hours of age was positive in some asymptomatic newborns (20).

Also, we did not test intrauterine tissue in our study for symptomatic mothers.

CONCLUSION

In conclusion, COVID-19 infection in neonates has different presentations considering mostly respiratory symptoms and subsequent radiographic features of a viral pneumonia and effective response to oxygen therapy. The symptoms were by far less severe in newborns, although we lost two cases to this infection. This highlights the necessity for good COVID-19 prognosis in infants and neonates.

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