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ORIGINAL ARTICLE

Maternofetal outcome and six months follow-up of pregnant patients with COVID-19 ARDS

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Abstract

Objective: In this study, it was aimed to evaluate pregnant patients followed in the intensive care unit (ICU) with severe acute respiratory distress syndrome due to COVID-19.

Material and methods: In this study, all pregnant patients infected with COVID-19 who were admitted to the ICU with the diagnosis of acute respiratory distress syndrome (ARDS) were evaluated retrospectively. Demographic, laboratory and clinical findings and follow-up of the mother and newborn at least 6 months after discharge were recorded.

Results: A total of 17 patients were included in this study. Three of the patients died in the ICU, 13 patients were discharged, 1 patient is still being followed up in the palliative care unit. 14 of 17 patients required mechanical ventilation and 11 patients were extubated. All patients had not been vaccinated. We detected tracheal stenosis in four of the eleven patients who were intubated and survived.

Conclusions: While managing pregnant patients with respiratory failure, making decisions about delivery timing remains the most controversial. Based on our experience, we can say that if the week of gestation is compatible with life, the decision to deliver should be taken before severe progression of the mother's respiratory distress. Tracheal stenosis formation caused by intubation should be suspected even in short intubation periods in pregnant patients. In this, the addition of factors such as giving prone position, not following appropriate cuff pressure to physiological changes in pregnancy is involved.

Keywords: Pregnancy, Covid-19, intensive care

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Introduction

In late December, 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, China,with clinical presentations resembling those of viral pneumonia. Afterward, the virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly leading to a global pandemic that cause clogging of the healthcare system [1]. All the countries were coping with the COVID-19 outbreak; hence, elective surgical procedures were postponed or cancelled except deliveries. We know that symptomatic pregnant patients who have tested positive for SARS-CoV-2 are at a higher risk of developing acute respiratory distress syndrome and adverse perinatal events(invasive ventilation, prematurity) than non-pregnant patients [2-7]. Underlying comorbidities, especially advanced maternal age and obesity seem to be the risk factors causing critical illness.

Understanding the clinical course of COVID-19 in the pregnant population is vital for deciding a suitable approach care for two patients; mother and fetus. Physiological alterations including pulmonary, cardiovascular and immunological alterations make it difficult to manage a pregnant patient [8]. It is important to know that pregnant patients with ARDS require care from the team work of experienced staff. During COIVID-19 pandemic, intensivists and obstetricians learned about the importance of close communication and making decisions together especially during delivery time; however, this decision process remains controversial.

We hope to contribute to this need, presenting the clinical features and six-months follow up of 17 pregnant patients who were infected with SARS-CoV-2 and admitted to the ICU. We aimed to explain clinical manifestations including invasive or non-invasive mechanical ventilation, prone positioning, medical and all other alternative therapies and laboratory findings.

Material and Methods

This is a retrospective, observational, single center study. In this study, those symptomatic pregnant patients were included who were admitted to the ICU between August 2020 and December 2021, with a positive result for SARS-CoV-2.After obtaining the approval of the ethics committee, with number 16.01.2023/1, the demographic, laboratory and clinical findings of those patients were recorded and at least a six-months follow-up after discharge of the mother and newborn was questioned.

Patients

This study included pregnant patients who had respiratory failure and ventilation requirements with a positive RT- PCR test result at different stage of the pregnancy trimester. Patients who were admitted to the ICU with an advanced oxygen demand (i.e. high flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIMV) or mechanical ventilation) were considered.

Statistical analysis

Normally distributed data are presented as the mean±standard deviation for numerical variables. The number of patients *(n)* and the proportions (%) were calculated for the categorical variables.

Results

A total of 17 patients were included in this study. Three of the patients died in the ICU, 13 patients were discharged, 1 patient is still being followed up in the palliative care unit. 14 of 17 patients required mechanical ventilation and 11 patients were extubated.

ICU period

The mean age of the patients was 31.8±4.6 years in surviving patients and 31.3±7.6 years in non-surviving patients. The mean body mass index (BMI) was 30.3±2.3 and 30.7±7.1 kg/m2 in surviving and non-surviving patients, respectively. No preexisting disease was found in 14 patients, whereas two patients had hypothyroidy and diabetes mellitus and one patient had hypertension and diabetes mellitus. Cough, dyspnea and myalgia were the symptoms that were most frequently reported by these patients. None of the patients had been vaccinated. The demo-biographic characteristics of these patients are presented in Table 1.

Six patients were nulliparous and others multiparous. Only one patient was in the second trimester, while all others were in the third trimester. The delivery gestation week was 32 weeks 6 days for surviving patients and 28 weeks 1 day for non-surviving patients. All patients had undergone cesarean section during the

ICU follow-up except two. One patient was discharged in the 27th week and delivered in term by cesarean section. Another pregnant patient was discharged in the 24th week, but she had cardiopulmonary arrest 5 days after her discharge. She was followed in the ICU until cesarean section in 33 weeks. Unfortunately, she had hypoxic ischemic encephalopathy and was tracheostomized in room air.

In 14 patients, invasive ventilation was required and all these intubated patients and except one who was in the second trimester had cesarean section in 24 hours after intubation. The average invasive ventilation time was 6.7±5.7 days in surviving patients and 22.6±3.2 days non-surviving patients. We applied prone position even before deliveryby supporting pregnancy belly to those who needed invasive ventilation and had PaO_2 / FiO_2 ratio under 150 or oxygen demand more than 60 % FiO_2. Three patients did not need invasive ventilation; they were stable with HFNC and NIMV. The average length of hospital stay was 25.5 ±6.6 days in surviving patients and 30.3±7.2 days in non-surviving patients. Three patients underwent immune plasma therapy; eight patients underwent treatment through remdesivir; nine patients underwent treatment through favipiravir; one patient underwent anakinra therapy. In two patients remdesivir therapy ceased because of increased liver enzymes. Fifteen patients underwent prednisolone pulse therapy, with 250 mg/day for three days.

In laboratory findings, we recorded aspartate transaminase (AST), C-reactive protein (CRP),

Table 1. Demo /biographic data of the patients and their newborns (mean SDwith median)

	Survival (n=14)	Non-survival (n=3)
Age(years)	31.8±4.6	31.3±7.6
Underlying diseases		
Diabetes Mellitus	4	None
Hypertension	1	None
Hypothyroidy	2	None
Coronary artery disease	None	1
Epilepsy	1	
BMI (kg/m2)	30.3±2.3	30.7±7.1
Parity		
Multiparous	9 2	2
Nulliparous	5 1	1
SARS-CoV-2 confirmative RT-PCR*	All	All
Gestational week on admission	30 weeks 4 days	27 weeks 1 day
Gestational week at birth	36 weeks 6 days	28 weeks 1 days
Birth weight (grams)	2034.6±772.2	1123.3±184.6
APGAR score (1st and 5th min)	1st6±2.3 5th 7.42±1.5	1st2±3.4 5th 3.6±3
SARS-CoV-2 confirmative RT-PCR	Four neonates have test with negative result	One neonate has test with negative result
NICU* stay (day)	27.2±22.9	101±40.5
Surviving newborn	13	3
Non-surviving newborn	1	

lactate dehydrogenase (LDH) and ferritin levels for all patients. High CRP and ferritin levels at admission were remarkable. When we analyzed these data with clinical findings, we could say interpret that the patients presented with macrophage activation syndrome. We performed thoracic tomography in 12 patients and multifocal ground glass opacities observed in 10 patients. In two patients we applied extracorporeal membrane oxygenation (ECMO). Unfortunately, neither of them survived. All clinical and laboratory findings are presented in Table 2.

Clinical course of newborns

A total of 16 neonates were admitted to the neonatal intensive care unit (NICU). The average birth weight of surviving newborns was 2034.6±777.2 g, while that of non-survivors was 1123±184.6 g. When the Appearance-Pulse-Grimace-Activity-Respiration (APGAR) scores of newborns were evaluated, the mean APGAR scores of survivorswere 6±2.3 and 7.4±1.5, while that of non-survivors was 2±3.4 and 3.6±3 for the first and fifth minutes. In the NICU, the length stay of babies of the surviving mothers was 27.2±22.9 days, while that of the non-surviving mothers was 101±40.5 days. All neonates survived and were discharged except the one whose mother who was in custody. We present the peripartum findings of the mother and fetus in Table 1.

Six months follow-up period

We had telephonic conversations with all patients at six months of recovery and none of them refused to answer our questions. Hence 13 patients agreed to participate, one surviving patient was still in the palliative care unit

Table 2. Clinical and laboratory findings

	Survival (n=14)	Non-survival (n=3)
Symptoms		
Dyspnea	10	2
Cough	12	3
Fever	3	None
Invasive ventilation (day)	6.7±5.7	22.6±3.2
Length of stay (day)	25.5±6.6	30.3±7.2
Prednisolone (250 mg/3 days)	13	2
Anti-viral therapy		
Remdesivir*	6	2
Favipiravir**	4	1
Ritonavir/Lopinavir	6	2
Immune plasma therapy	3	None
ECMO	None	2
CT Scan	n=9	n=1
Ground glass opacity	9	1
Embolism	None	None
Echocardiography	n=5 Normal findings	n=2 Normal findings
Laboratory findings on admission		
CRP (mg/L)	87.2 ±56	117±3.6
Lymphocyte (10^9/L)	0.81±0.39	0.6±0.3
LDH (u/L)	436±206	378±129.4
Ferritin (µ/L)	192.7±247.9	175±103.9
AST (u/L)	58.5±86.3	207.6±142.6

*In two patients remdesivir therapy was stopped because liver enzymes were elevated.

**If compassionate use of remdesivir was not available we applied favipiravir after delivery.

Table 3. Patients' findings on at least 6 months after recovery (number of patients=13)

	Yes (n)	No (n)
Cough	5	8
Dyspnea	2	11
Hospital admission	5	8
Re-COVID infection	2	11
COVID-19 vaccination mRNA vaccine Attenuated vaccine	 11 2	
Sleeping disorder	6	7
Psychiatric medication	1	12

at the time. Eight patients had no pulmonary symptoms during their daily activities. Five patients were admitted to the hospital with cough and myalgia after recovery and two were diagnosed tracheal stenosis and were hospitalized. All patients had been vaccinated with COVID-19 vaccines, 11 had mRNA vaccine and 2 had attenuated vaccines. Two patients had mild COVID-19 re-infection with no hospitalization. Six patients complained of fear of death and accompanying insomnia and anxiety, and one patient complained of claustrophobia. However, only one patient was found to be taking medication for depression.

Three patients were admitted to the hospital with complaints of cough and shortness of breath 1-3 weeks after discharge. One of them had a cardiopulmonary arrest in the emergency room. In the other 2 patients, stenosis was detected and underwent single-stage corrective surgery. We suspected stenosis during weaning from invasive ventilation in one another patient and had a CT scan. Tracheal stenosis was diagnosed and patient had surgery. On the phone call, three of them were asymptomatic, one was still in palliative unit, tracheostomized but in room air.

Discussion

Physiological changes in the respiratory and circulatory systems and alterations in immunology make pregnant patients more vulnerable to viral infections [8]. Pregnant patients are more susceptible to severe respiratory infections because of the reduction in total lung capacity and the inability to clear secretions especially in the third trimester [9]. A study of 91,412 women who tested positive for SARS-CoV-2 demonstrated that the most frequently reported symptoms were cough, shortness of breath and muscle pain. In the same study, substantially higher percentage of pregnant patients than nonpregnant patients was hospitalized and admitted to the ICU [10]. Centers for Disease and Prevention (CDC) reported that pregnant patients were three times likelier to be admitted to an ICU, 2.9 times likelier to need invasive ventilation and 1.7 times likelier to die compared to nonpregnant patients including over 400,000 persons of reproductive age with symptomatic COVID-19 and adjusted for age, race and ethnicity, and underlying medical conditions [6].

In pregnant patients, because of sufficient fetal oxygenation resting oxygen saturation should be above 95% for pulse oximetry monitoring. We admitted the patients who had dyspnea and oxygen demand more than 10 l/min with nonrebreather mask to achieve spO_2 >95. Three patients did not need invasive ventilation and adequate oxygen saturation was achieved with HFNC and NIMV. It is still not clear whether delivery improves maternal outcome. Because this timing of delivery is controversial and has to be done by a fetomaternal team, including an intensivist, obstetrician and neonatal intensivist. Certainly, fetal maturation is important; however, delivery before maternal decompensation can help a patient with respiratory failure. We did not wait for the progression of pregnant patient's respiratory distress and the mean delivery time was 31 weeks. We thought that not to wait for

delivery until maternal decompensation might be a good decision.

Prone positioning was routinely performed earlier after intubation in patients with PaO_2 / FiO_2ratio <150 and FiO_2>60% and was continued for about 16 hours in a day or more. By supporting the patient from appropriate points, the prone position can be applied safely in the second and third trimesters. Horrey and et al. clearly explained these supports in their study [11]. If the patient does not benefit from invasive ventilation and prone position (ECMO) should be considered [12]. In two patients, we set up ECMO, unfortunately neither survived.

We know that pregnant women especially those older than 35 years are usually in a hypercoagulable state, so current guidelines recommend that all pregnant women with confirmed COVID-19 should have thromboprophylaxis during the antenatal and postnatal period [12-14]. In our clinic all patients were treated with enoxaparin twice a day by calculating the dose according to weight, D-Dimer level and any risk factor.

In pregnant patients, there is a trend to use remdesivir and lopinavir-ritonavir for antiviral therapy. All patients who were hospitalized before admission to the ICU were treated with lopinavir-ritonavir. In the ICU, we preferred compassionate use of remdesivir in eight patients. However, because of the elevated liver enzymes in two patients, we had to discontinue it.

In late 2020, one year after the first case, US Food and Drug Administration approved messenger RNA (mRNA) vaccines for emergency use. However, there is not enough data about whether this vaccine has been approved to be used in pregnancy. The Royal College of Obstetricians and Gynecologists (RCOG) recommend vaccination without specification of gestation but if pregnant patients have a lower risk for severe disease, vaccination may be delayed until the second trimester [15]. In our study, none of the patients was vaccinated before or during pregnancy. After recovery, all of them chose to receive the COVID-19 vaccine, mRNA or attenuated vaccine. It is thought that COVID-19 vaccines may be beneficial in reducing the risk of severe disease and mortality in pregnant patients [16-17]. However, more research is needed for the approval of COVID-19 vaccines in pregnancy.

In the ICU, subglottic/tracheal stenosis or malaise are serious life-threatening conditions resulting from ischemia caused by intubation [18]. Prolonged duration of intubation time and prone position may facilitate the development of stenosis, especially in pregnant patients who have edematous upper airways. We found tracheal stenosis in our pregnant patients at a frequency that we had not seen in other patients who had undergone invasive ventilation and prone positioning. Tracheal stenosis should be kept in mind in patients who present with stridor or shortness of breath and have a history of intubation, and treatment of such patients should not be delayed.

The disadvantage of the most limiting aspect of the study was the small sample size and the absence of a control group.

Conclusion

While managing pregnant patients with respiratory failure, making decisions about delivery timing remains the most controversial. Based on our experience, we can say that if the week of gestation is compatible with life, the decision to deliver should be taken before severe progression of the mother's respiratory distress. Tracheal stenosis formation caused by intubation should be suspected even in short intubation periods in pregnant patients.

Informed Consent: The written informed consent was taken from participants and their parents.

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