Outcomes of mechanical ventilation in COVID-19 pregnant patients

Mihajlovic S[1,2], Savic P[3,4], Potparevic N[1], Lackovic M[1]

[1]Department of Obstetrics and Gynecology, University hospital "Dr. Dragisa Misovic"
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, University of Belgrade
[3]Department of General Surgery, University hospital "Dr. Dragisa Misovic"
[4]Department of Surgery and Anesthesiology, Faculty of Medicine, University of Belgrade
Belgrade, Serbia

Abstract

Background: Pregnancy poses a risk factor for respiratory infections due to hormonal changes, reduced tolerance to hypoxia, immunodeficiency, and increased susceptibility towards viral infections. Pregnant women might develop a broad spectrum of clinical conditions associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, from asymptomatic to potentially life-threatening complications. Critical respiratory failure associated with the progression of viral pneumonia is the most severe complication of the coronavirus disease (COVID-19). In some cases, it may require intubation and invasive mechanical ventilation.

Case series: In this case series, we evaluated the outcomes and clinical features of eight critically ill pregnant patients requiring invasive mechanical ventilation during treatment. The most commonly observed symptoms were fever at admission to the hospital, cough, difficulty breathing, and fatigue. Less frequently observed were sore throat and loss of smell and taste. All patients had anemia, and hypertension was the second most common comorbidity in pregnancy. Pregnant patients with lethal outcomes were older than those who recovered. They had higher body mass index values, more symptoms at admission, and higher C-reactive protein values and ferritin levels. Acute Respiratory Distress Syndrome (ARDS) was diagnosed in five cases, and none of these patients survived.

Conclusion: Obesity, maternal age, and diagnosis of ARDS were most commonly observed in our group of patients with lethal outcomes. Preventive measurements, counseling, and enlightenment of potential risk factors, such as obesity, advanced maternal age, and pregnancy-related comorbidities, should be the cornerstones in crises such as COVID-19 when medical care and resources are limited or restricted. HIPPOKRATIA 2022, 26 (1):32-37.

Keywords: Coronavirus disease, COVID-19, pregnancy, respiratory failure, mechanical ventilation, critical care, outcomes

Corresponding author: Milan Lackovic, MD, PhD, Milana Tepica 1, 11000, Belgrade, Serbia, tel: +381113630700, fax: +381113672025, e-mail: lackovic011@gmail.com

Introduction

In this dynamic world of needs, hopes, and dreams, where new boundaries and limits are constantly set and pushed forward, and everything has become relative, human life and even our existence have suddenly become seriously threatened by the presence of a new, unknown enemy, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Suddenly, fear of the unknown shaped the efforts to protect fundamental human needs and rights. This fear unsettles human nature, especially for pregnant women who are bringing new life to this world, a life that might have been endangered even before it was brought to this world, and a world where nothing is the same.

During the last three years, maternal morbidity and mortality data regarding the coronavirus disease (COVID-19) pandemic has dramatically changed. From the initial point of view that pregnancy poses some protective features, it is now known that pregnant women might develop a wide spectrum of clinical features, from asymptomatic to life-threatening complications associated with the SARS-CoV-2 infection[1]. Critical respiratory failure associated with viral pneumonia progression might lead to acute respiratory distress syndrome (ARDS), which is one of the most severe COVID-19 infection complications. In order to preserve vital functions, invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) is often required[2].

Due to hormonal changes, reduced tolerance to hypoxia, immunodeficiency, and increased susceptibility towards viral infection, pregnancy poses a risk factor for the progression of respiratory infection[3]. Compared

to non-pregnant women of reproductive age, pregnant COVID-19 patients are more likely to be hospitalized, be transferred to intensive care units (ICU), and ultimately require intubation and mechanical ventilation management[4]. Several risk factors have been identified and are considered relevant to distinguish low from high-risk patients to provide better triage and timely treatment. Advanced maternal age, preexisting medical conditions, pregnancy-related comorbidities, obesity, race, and ethnicity are among the most common ones[5].

Since devastating consequences are closely related to COVID-19 infection and the vulnerable state of pregnancy[3,4], it is imperative to provide a timely, efficient, and safe therapeutic approach for all pregnant women. Experiences with antiviral and immune-modulating therapy have proven reassuring profiles regarding their safety, but an individualized approach and possible adverse events must be addressed[6]. mRNA vaccines have proven safe and effective in preventing severe infections. Therefore, advocacy for COVID-19 vaccination as the primary infection prevention among pregnant and reproductive-age women should be a high priority[7].

Reports regarding maternal outcomes among critically ill COVID-19-infected pregnant patients remain scarce, and it is essential to present and describe experiences from different centers. More knowledge benefits medical professionals caring for critically ill patients and might improve decision-making strategies. Therefore, our study aims to present experiences from one of Serbia's referral centers for COVID-19-positive patients during the SARS-CoV-2 pandemic.

Case series

In this series of cases, we have presented maternal outcomes and clinical features of eight consecutive critically ill pregnant patients requiring invasive mechanical ventilation as a measure of life support. Before their hospitalization, all patients were tested and had positive throat swabs for COVID-19 on quantitative real-time polymerase chain reaction. None of these patients was vaccinated.

Patients were treated in Serbia's referral center for COVID-19-positive patients, a tertiary health care center, the University Hospital "Dr. Dragisa Misovic" in Belgrade. The retrospective observational case series included patients hospitalized in ICU from March 2020 until November 2021, and it was retrospectively approved by the Institutional Review Board in August 2020 (No: 01-8816). We have included in the series all pregnant patients who required and received invasive mechanical ventilation during their course of treatment in our center. Patients were transferred to ICU, and eventually, invasive mechanical ventilation was initiated based on peripheral blood oxygen saturation, blood gas analysis, respiratory and heart rate, and systolic and diastolic blood pressure. In all eight cases, non-invasive mechanical ventilation was initially administered. Table 1 presents the general characteristics of admitted pregnant women and mechanical ventilation outcomes.

Table 2 presents the symptoms on admission to the hospital of pregnant women who tested positive on SARS-CoV-2, were transferred to ICU, and supported with invasive mechanical ventilation. Three out of eight patients had more than 50 % of tested symptoms on admission (52.6 %). Fever (body temperature >38 °C) on admission, cough, and systemic inflammatory response syndrome were present in all those patients (100 %). Difficulty breathing and fatigue were present in six out of eight patients (75 %). Less frequent were sore throat, loss of smell and taste (every fourth patient). The least frequent was abnormal uterine bleeding (12.5 %). Headache and diarrhea were absent in any admitted patient (0 %) (Table 2).

Table 3 presents the risk factors, and laboratory findings of the positive pregnant women transferred to ICU and supported with invasive mechanical ventilation. Regarding risk factors, it is shown that all pregnant women were diagnosed with anemia, while the second most frequent risk factor was hypertension (37.5 %). None of them had diabetes mellitus (0 %) (Table 3).

Table 1: General features and outcomes of invasive mechanical ventilation in eight pregnant COVID-19-positive patients transferred to the intensive care unit.

	Age (years)	Body Mass Index (kg/m²)	Symptoms onset (days) before hospitalization	Symptoms onset (days) to initiation of mechanical ventilation	Gestational age at admission (days)	Mechanical Ventilation outcome
Patient 1	42	25.26	7	7	224	Succumbed to illness
Patient 2	29	24.22	6	9	207	Recovered
Patient 3	32	30.12	5	5	252	Succumbed to illness
Patient 4	38	32.15	4	6	203	Succumbed to illness
Patient 5	33	27.70	8	10	248	Recovered
Patient 6	26	46.61	4	9	220	Succumbed to illness
Patient 7	30	32.27	5	7	221	Recovered
Patient 8	38	27.20	4	8	105	Succumbed to illness

Table 2: Symptoms on hospital admission of pregnant COVID-19-positive women transferred to the intensive care unit and supported with invasive mechanical ventilation.

Symptoms	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	number (percent)
Eye redness	No	No	No	No	No	No	No	No	0 (0 %)
Sore throat	Yes	No	No	No	No	Yes	No	No	2 (25 %)
Fever (>38 °C)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8 (100 %)
Cough	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8 (100 %)
Difficulty breathing	No	Yes	Yes	Yes	Yes	Yes	No	Yes	6 (75 %)
Headache	No	No	No	No	No	No	No	No	0 (0 %)
Arthromyalgia	No	No	No	No	No	No	No	No	0 (0 %)
Loss of smell	Yes	No	No	No	No	No	No	Yes	2 (25 %)
Loss of taste	Yes	No	No	No	No	No	No	Yes	2 (25 %)
Fatigue	No	Yes	No	Yes	Yes	Yes	Yes	Yes	6 (75 %)
Diarrhea	No	No	No	No	No	No	No	No	0 (0 %)
Arrhythmias	No	No	No	No	No	No	No	No	0 (0 %)
Loss of conciseness	No	No	No	No	No	No	No	No	0 (0 %)
ARDS	Yes	No	Yes	Yes	No	Yes	No	Yes	5 (62.5 %)
SIRS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8 (100 %)
Shock	Yes	No	Yes	Yes	No	Yes	No	Yes	5 (62.5 %)
MODS	Yes	No	Yes	Yes	No	Yes	No	Yes	5 (62.5 %)
Cardiac insufficiency	Yes	No	Yes	Yes	No	Yes	No	No	4 (50 %)
Abnormal uterine bleeding	No	Yes	No	No	No	No	No	No	1 (12.5 %)
number (percent)	10 (52.6 %)	6 (31.6 %)	8 (42.1 %)	9 (47.4 %)	5 (26.3 %)	10 (52.6 %)	4 (21.1 %)	10 (52.6 %)	

ARDS: Acute Respiratory Distress Syndrome, SIRS: Systemic Inflammatory Response Syndrome, MODS: Multiple Organ Dysfunction Syndrome.

Pregnant patients with lethal outcomes were older (35.20 ± 6.26 years), had higher body mass index (BMI) (32.27 ± 9.43), had more symptoms (9.40 ± 0.89), had more risk factors (1.80 ± 0.84), higher C-reactive protein (CRP) values (218.94 ± 83.85) and higher ferritin levels (388.20 ± 322.11) than those pregnant ICU patients who recovered. On the contrary, in pregnant ICU patients with lethal outcomes, lesser days to hospitalization from symptoms' onset (4.80 ± 1.30 days), lesser days to mechanical ventilation from symptoms' onset (7.00 ± 1.58 days), and lower gestational age on admission (200.8 ± 56.37 days) were noticed (Table 4).

Discussion

All patients in this case series were in critical condition due to progressive respiratory failure and pneumonia resulting from SARS-CoV-2 infection. Invasive mechanical ventilation was initiated after the various modes of non-invasive mechanical ventilation support failed to provide adequate oxygen supply.

Out of the eight pregnant women in this case series, lethal outcomes were registered in five cases. Initial reports from the beginning of the pandemic revealed that more than 90 % of patients in the general population who received invasive mechanical ventilation eventually died[8]. Outcomes among pregnant patients were more encouraging[9]. ARDS was diagnosed in five cases, and none of these patients survived. The oldest patient in this case series was 42 years of age, while the youngest was 26 years old. The average age of our patients was 33.5 years. Comparisons between the two groups, those recovered and decedent, suggest that women in the decedent group were nearly five years older.

Advanced maternal age is an individual risk factor for the progression of COVID-19 infection in pregnancy[5]. However, it often goes hand in hand with other comorbidities and chronic diseases, such as hypertension-related conditions and glucose intolerance[10]. Acquired cardiovascular diseases are often accompanied by diabetes, obesity, and advanced maternal age, and their management is often challenging[10]. Although COVID-19 infection does not increase the risk for hypertension-related conditions among pregnant women[11], it imposes an additional challenge in managing these patients. It led to rising maternal mortality rates during the pandemic[1]. Cardiac insufficiency and heart failure led to the death

Table 3: Risk factors and laboratory findings of pregnant COVID-19-positive women transferred to the intensive care unit and supported with invasive mechanical ventilation.

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	number (percent)
Risk factors									
Hypertension	No	No	Yes	Yes	No	Yes	No	No	3 (37.5 %)
Diabetes Mellitus	No	No	No	No	No	No	No	No	0 (0 %)
Thrombophilia	No	No	No	Yes	No	No	No	No	1 (12.5 %)
Anemia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8 (100 %)
number (percent)	1 (25 %)	1 (25 %)	2 (50 %)	3 (75 %)	1 (25 %)	2 (50 %)	1 (25 %)	1 (25 %)	
Laboratory findings									
Leucocytes ($10^3/\mu L$)	8.3	22	11.6	7.8	14.4	18.4	20.5	7.7	-
Lymphocytes (%)	5	16	11	5	5.7	8	3.4	4	-
Neutrophils (%)	86	81	64	91	91.3	76	94.8	90	-
Monocytes (%)	3	2.8	5	3.5	2.9	7	1.6	5	-
Thrombocytes ($10^3/\mu L$)	252	218	279	241	217	260	251	140	-
C- Reactive Protein	353	217.7	214	126.2	131.5	221.5	176.6	180	-
Ferritin (ng/mL)	280	249	889	56	240	216	204	500	-
D dimer (mg/L)	7.7	21.71	5.76	5	15.18	7.16	1.61	3	-

Table 4: Distribution of observed variables regarding treatment outcome (positive pregnant patients who recovered or succumbed to illness after invasive mechanical ventilation in the intensive care unit).

	Recovered	Succumbed to illness
	mean ± SD (95 % CI)	mean ± SD (95 % CI)
Age (years)	30.67 ± 2.08 (25.50-35.84)	35.20 ± 6.26 (27.43-42.97)
Body Mass Index (kg/m^2)	28.06 ± 4.04 (18.03-38.09)	32.27 ± 9.43 (19.56-42.98)
Symptoms onset (days) before hospitalization	6.33 ± 1.53 (2.54-10.13)	4.80 ± 1.30 (3.18-6.42)
Symptoms onset (days) to initiation of mechanical ventilation	8.67 ± 1.53 (4.87-12.46)	7.00 ± 1.58 (5.04-8.96)
Symptoms Number on admission	5.00 ± 1.00 (2.52-7.48)	9.40 ± 0.89 (8.29-10.51)
Gestational age on admission (days)	225.33 ± 20.84 (173.56-277.10)	200.80 ± 56.37 (130.81-270.79)
Number of risk factors	1.00 ± 0.00 (1.00-1.00)	1.80 ± 0.84 (0.76-2.84)
Leucocytes ($10^3/\mu L$)	18.97 ± 4.03 (8.97-28.97)	10.76 ± 4.56 (5.10-16.43)
Lymphocytes (%)	8.37 ± 6.71 (-8.30-25.04)	6.60 ± 2.88 (3.02-10.18)
Neutrophils (%)	89.03 ± 7.17 (71.21-106.85)	81.40 ± 11.39 (67.25-95.55)
Monocytes (%)	2.43 ± 0.72 (0.64-4.23)	4.70 ± 1.57 (2.76-6.64)
Thrombocytes ($10^3/\mu L$)	228.67 ± 19.35 (180.60-276.73)	234.40 ± 54.56 (166.65-302.15)
C- Reactive Protein	175.27 ± 43.12 (68.16-282.37)	218.94 ± 83.85 (114.83-323.05)
Ferritin (ng/mL)	231.00 ± 23.81 (171.85-290.15)	388.20 ± 322.11 (-11.75-788.15)
D dimer (mg/L)	12.83 ± 10.25 (-12.64-38.30)	5.72 ± 1.87 (3.41-8.04)
Mechanical Ventilation outcome number (percent)	3 (37.5 %)	5 (62.5 %)

SD: standard deviation.

of four patients in our case series. Three were previously diagnosed with a hypertensive disorder; one patient had gestational hypertension, and two suffered from chronic hypertension. None of our patients was diagnosed with pregestational or gestational diabetes. In Serbia, organized screening for gestational diabetes is performed between the 24th and 28th week of gestation, but due to the COVID-19 crisis, the screening procedure was not performed, which partially explains the lack of gestational diabetes diagnosis; more importantly, it emphasizes the

importance of screening procedure and consequences that pandemic has had on perinatal care in Serbia. Other countries have experienced similar challenges regarding compromised perinatal care, and valuable experiences have taught us to prioritize childbearing people and strive for high-quality maternal care[12].

Obesity remains a global health threat among modern-age men and women, and it is the denominator for metabolic and chronic diseases[13]. Seven patients had BMI values beyond recommended, and four of them were obese, including one patient with class III obesity. The BMI discrepancy was apparent between the two compared groups. Patients in the recovered group were averagely overweight (average BMI: 28.06 ± 4.04 kg/m^2), and patients in the decedent group were mainly obese (average BMI: 32.27 ± 9.43 kg/m^2), a difference that might pose a significant strategic approach in triage and treatment planning. Furthermore, the only patient who successfully recovered and continued her pregnancy is, at the same time, the only patents whose BMI value was below 25 kg/m^2. Obesity leads to a chronic inflammatory state, interferes with cellular immune response, and might increase antiviral, anticoagulant, and antibacterial resistance[14]. Obesity is recognized among pregnant women as a key comorbidity and risk factor for disease severity and even with negative survival prognosis[14,15].

The decedent patients group had twice as many symptoms on hospital admission and nearly the same percentage of risk factors. From the begging of the pandemic, pregnant patients with multiple COVID-19-related symptoms on admission were at higher risk of severe COVID-19 infection[16]. This group of patients also had a shorter time between the symptoms onset and hospitalization commencement, and this important fact should raise awareness that these patients must be closely monitored. Preventive hospitalization should be considered when providing adequate monitoring for outpatients is impossible.

All presented laboratory results mentioned above were collected on the day of the initiation of mechanical ventilation. More progressive lymphopenia and neutrophilia were observed in the group of decedent patients. These findings agree with data from existing literature regarding COVID-19 manifestations and the progression of COVID-19 infection[17]. All patients in our series were anemic, and anemia is a well-known risk factor for the severity of COVID-19 infection and poor pregnancy outcome[1,4]. Hyperferritinemia is associated with excessive inflammatory reactions and higher mortality rates[18]. Ferritin levels were more than 50 % higher in the decedent group compared to the recovered group of patients. Therefore, this marker of infection must be closely assessed along with the patient's clinical condition to guide clinicians and ensure rapid patient assessment and management.

Susceptibility for COVID-19 infection is closely associated with the third trimester of pregnancy[19]. The mean gestational age at delivery was 33 weeks and four days. Emergency cesarean section was performed in six cases, one pregnancy was successfully continued, and a patient at 16th weeks of gestation died before the pregnancy was terminated. Six live preterm newborns were transferred to the neonatal ICU for further treatment, and they all had negative swabs for SARS-CoV-2 infection.

The main limitation of this case series is the small sample size. Due to the low number of enrolled pregnant women, it was impossible to draw statistical conclusions. Another limitation is that all patients in these case series belong to the Serbian population.

Patients in this case series were critically ill and of the same race and ethnicity belonging to the Serbian population. Obesity, maternal age, and diagnosis of ARDS were most commonly observed in patients with lethal outcomes. Preventive measurements, counseling, and enlightenment of potential risk factors, such as obesity, advanced maternal age, and pregnancy-related comorbidities, should be the cornerstones in crises such as COVID-19 when medical care and resources are limited or restricted.

Conflict of Interest
The authors certify that there is no conflict of interest.

References
1. Lokken E, Huebner EM, Taylor GG, Hendrickson S, Vanderhoeven J, Kachikis A, et al. Disease severity, pregnancy outcomes, and maternal deaths among pregnant patients with severe acute respiratory coronavirus 2 infection in Washington State. Am J Obstet Gynecol. 2021; 225: 77.e1-77.e14.
2. Wu D, Fang D, Wang R, Deng D, Liao S. Management of Pregnancy during the COVID-19 Pandemic. Glob Chall. 2020; 5: 2000052.
3. Ferrer-Oliveras R, Mendoza M, Capote S, Pratcorona L, Esteve-Valverde E, Cabero-Roura L, et al. Immunological and physiopathological approach of COVID-19 in pregnancy. Arch Gynecol Obstet. 2021; 304: 39-57.
4. Brandt JS, Hill J, Reddy A, Schuster M, Patrick HS, Rosen T, et al. Epidemiology of coronavirus disease 2019 in pregnancy: risk factors and associations with adverse maternal and neonatal outcomes. Am J Obstet Gynecol. 2021; 224: 389.e1-389.e9.
5. Pineles BL, Goodman KE, Pineles L, O'Hara LM, Nadimpalli G, Magder LS, et al. Pregnancy and the Risk of In-Hospital Coronavirus Disease 2019 (COVID-19). Obstet Gynecol. 2022; 139: 846-854.
6. Favilli A, Mattei Gentili M, Raspa F, Giardina I, Parazzini F, Vitagliano A, et al. Effectiveness and safety of available treatments for COVID-19 during pregnancy: a critical review. J Matern Fetal Neonatal Med. 2022; 35: 2174-2187.
7. Halasa NB, Olson SM, Staat MA, Newhams MM, Price AM, Pannaraj PS, et al. Overcoming Covid-19 Investigators. Maternal Vaccination and Risk of Hospitalization for Covid-19 among Infants. N Engl J Med. 2022; 387: 109-119.
8. Luo M, Cao S, Wei L, Zhao X, Gao F, Li S, et al. Intubation, mortality, and risk factors in critically ill Covid-19 patients: A pilot study. J Clin Anesth. 2020; 67: 110039.
9. Easter SR, Gupta S, Brenner SK, Leaf DE. Outcomes of Critically Ill Pregnant Women with COVID-19 in the United States. Am J Respir Crit Care Med. 2021; 203: 122-125.
10. Ramlakhan KP, Johnson MR, Roos-Hesselink JW. Pregnancy and cardiovascular disease. Nat Rev Cardiol. 2020; 17: 718-731.
11. Gulersen M, Rochelson B, Shan W, Staszewski C, Bornstein E, Blitz MJ. The association of hypertensive disorders of pregnan-

cy with severe acute respiratory syndrome coronavirus 2 infection. Am J Obstet Gynecol. 2022; 226: S154-S155.

12. Combellick JL, Basile Ibrahim B, Julien T, Scharer K, Jackson K, Powell Kennedy H. Birth during the Covid-19 pandemic: What childbearing people in the United States needed to achieve a positive birth experience. Birth. 2022; 49: 341-351.

13. Andreou E, Hajigeorgiou P, Kyriakou K, Avraam T, Chappa G, Kallis P, et al. Risk factors of obesity in a cohort of 1001 Cypriot adults: An epidemiological study. Hippokratia. 2012; 16: 256-260.

14. Petrakis D, Marginǎ D, Tsarouhas K, Tekos F, Stan M, Nikitovic D, et al. Obesity - a risk factor for increased COVID-19 prevalence, severity and lethality (Review). Mol Med Rep. 2020; 22: 9-19.

15. Földi M, Farkas N, Kiss S, Dembrovszky F, Szakács Z, Balaskó M, et al. Visceral Adiposity Elevates the Risk of Critical Condition in COVID-19: A Systematic Review and Meta-Analysis. Obesity (Silver Spring). 2021; 29: 521-528.

16. London V, McLaren R Jr, Atallah F, Cepeda C, McCalla S, Fisher N, et al. The Relationship between Status at Presentation and Outcomes among Pregnant Women with COVID-19. Am J Perinatol. 2020; 37: 991-994.

17. Oshay RR, Chen MYC, Fields BKK, Demirjian NL, Lee RS, Mosallaei D, et al. COVID-19 in pregnancy: a systematic review of chest CT findings and associated clinical features in 427 patients. Clin Imaging. 2021; 75: 75-82.

18. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Lab Anal. 2020; 34: e23618.

19. Mirbeyk M, Saghazadeh A, Rezaei N. A systematic review of pregnant women with COVID-19 and their neonates. Arch Gynecol Obstet. 2021; 304: 5-38.