Case Series

MATERNAL DEATHS CAUSED BY COVID-19 INFECTION IN THE FIRST YEAR OF THE PANDEMIC WAVE

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ABSTRACT

This article presents seven cases of maternal deaths attributed to COVID-19 during the first year of the pandemic wave. These cases provide insights into the natural progression of COVID-19 in pregnant women who were not vaccinated. This study showed that COVID-19 significantly increased maternal and neonatal mortality and morbidity. All of the patients exhibited symptoms of fever, cough, and dyspnea upon admission to the hospital. They were admitted with elevated respiratory rates (26–32 times/minute) and low oxygen saturation (<95%). Four patients had obesity, while one patient had pregestational diabetes. The COVID-19 diagnosis was established using a rapid antibody or antigen test and chest X-ray, which indicated pneumonia. Medical interventions administered to the patients included antiviral therapy (5 patients), antibiotics (6 patients), and anticoagulants (4 patients). From a total of five babies delivered, four babies were delivered via cesarean section. Two babies were not delivered due to previability and maternal deaths before delivery. The patients passed away within 3–10 days of hospital admission. In conclusion, adequate and early intervention and management of pregnant women infected with COVID-19 are crucial in preventing maternal and neonatal deaths, especially in unvaccinated women.

Keywords: COVID-19; maternal mortality; maternal health; pregnancy

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Highlights:
1. These cases of maternal deaths caused by COVID-19 infections illustrated the significant risk factors for maternal mortality during the early phases of the pandemic, while studies had not extensively reported this.
2. COVID-19 infections increase the risk of maternal and neonatal mortality, with infants having a lower chance of survival even if they are delivered.
3. Respiratory support, antiviral medications, antibiotics, anticoagulants, and supportive care are the primary treatments for severe COVID-19 in pregnancy.

INTRODUCTION

The COVID-19 pandemic has lasted for several years and created a huge health impact around the world. COVID-19 had infected a total of 109,167,919 people worldwide as of February 2021, with a mortality rate of 2,406,669 people (Worldometer 2021). Pregnant women become a high-risk population due to the anatomic, physiologic, hormonal, and immunologic changes during pregnancy. Anatomic and physiologic changes in the lung and chest during pregnancy

decrease maternal tolerance to hypoxia. Changes in the cell-mediated immune response during pregnancy will also increase the susceptibility of pregnant women to viral infection (Zaigham & Andersson 2020). Previous studies showed that COVID-19 increased morbidity during pregnancy, but the mortality rate was still quite low. In a meta-analysis study by Allotey et al. (2020), COVID-19 increased the risk of adverse pregnancy outcomes, including preterm delivery, preterm premature rupture of the membrane (PPROM), a higher cesarean section rate, hemorrhage postpartum, intrauterine fetal death (IUFD), neonatal death, and an abnormal Apgar score. Conditions such as postpartum hemorrhage and unviable gestational age can be direct and indirect causes of death in pregnant women. The percentage of maternal mortality caused by COVID-19 in a previous study was 0.1%, with 76 mortality cases in 11,580 pregnancies (Allotey et al. 2020, Sulistyono et al. 2020). A study by Zaigham & Andersson (2020) found no maternal deaths in a total of 108 pregnancy cases with COVID-19. However, we found from our study that COVID-19 significantly increased the risk of maternal death by eightfold. Vaccination status is a crucial prognostic indicator for COVID-19-infected maternal deaths. In our previous study, all of the mothers were unvaccinated against COVID-19 because the government had not yet implemented vaccination programs at the time (Akbar 2021, Akbar et al. 2022).

Until early 2021, Indonesia had become one of the Southeast Asian countries with the fastest-developing COVID-19 cases. The official data from the Indonesian Ministry of Health revealed that the total number of cases of COVID-19 was 1,210,000, with a mortality rate of 32,936 people. The percentage of the fatality rate was 3.12%. The average daily number of new cases in Indonesia was 10,000 cases per day in early 2021 (Satuan Tugas Penanganan COVID-19 2020). Rumah Sakit Universitas Airlangga is a teaching hospital that has become a referral center for maternal COVID-19 in Surabaya, Indonesia. Until mid-2021, Rumah Sakit Universitas Airlangga had delivered more than 300 cases of pregnancy with suspected COVID-19. In this case series, we present seven maternal deaths directly caused by COVID-19 at Rumah Sakit Universitas Airlangga.

CASE SERIES

We chose seven cases of maternal deaths caused by COVID-19 infection during pregnancy in the first year of the pandemic. During this early phase of the pandemic, no mothers had received the COVID-19 vaccine because the government had not yet implemented the program. All patients presented with a fever, cough, and dyspnea. The patients upon admission had increased respiratory rates (between 26 and 36) and low oxygen saturation (95%), which were indicative of dyspnea. Rapid antibody tests (n=6), rapid antigen tests (n=2), and chest X-rays (n=7) were utilized to diagnose all patients. The patients were treated with pharmacological and non-pharmacological treatments, as well as obstetric care. As a medical intervention, the patients received antiviral therapy (n=5), antibiotics (n=6), and anticoagulants (n=4). Five infants were delivered, four of them by cesarean section. However, two infants were not delivered due to previability (less than 24 weeks), and maternal and fetal mortality occurred prior to delivery. Only three infants survived and were then discharged from the hospital. The three others were stillbirths, and one infant passed away an hour after birth. One patient experienced postpartum hemorrhage following a cesarean section due to uterine atony and required a hysterectomy. The length of stay in these cases ranged from four to ten days.

Case 1

A 38-year-old woman, Mrs. J, was a multiparous patient with a gestational age of 33–34 weeks. She was referred to the hospital with complaints of fever in the last two weeks, coughing, and shortness of breath for a week. The current pregnancy was her second, with a previous history of sectio caesarea (SC) 10 years ago. During the physical examination, we found that the oxygen saturation was 60%, with a fast respiration rate of 32 breaths per minute. The results of COVID-19 screening showed positive immunoglobulin M (IgM) antibodies and an increased neutrophil-to-lymphocyte ratio (NLR), while the chest radiograph showed bilateral pneumonia. The patient also had a comorbidity of class II obesity. We treated the patient with 15 L/min oxygen supplementation using a non-rebreathing mask and medicines, i.e., oseltamivir, levofloxacin, and other supportive therapy. The next day, the patient showed signs of respiratory failure (oxygen saturation of 86.3%), so we decided to put her on a ventilator and perform an emergency SC to improve her condition. A baby girl was born with a 1,960-g body weight, 46-cm body length, and an Apgar score of 7–8. After the surgery, the mother's condition continued to deteriorate. Two days postoperatively, the patient showed worsened respiratory failure (70% saturation) and decreased consciousness, with a Glasgow Coma Scale (GCS) score of 111. We performed chest compression for five cycles, but it was unsuccessful, and the patient died.

Case 2

A 28-year-old woman, Mrs. LH, was 21–22 weeks pregnant and referred to the hospital with complaints

of coughing and shortness of breath for three days. At the previous hospital, the patient had symptoms of impending respiratory failure, with a respiration rate of 32 breaths per minute and 77% oxygen saturation. Previously, the anesthesiologist performed intubation, put the patient on a ventilator, and referred the patient to our hospital because the intensive care unit (ICU) was fully occupied. On arrival, the patient was already on a ventilator with a positive end-expiratory pressure (PEEP) of 8, a 100% fraction of inspired oxygen (FiO2), and a 95% oxygen saturation. This was the patient's second pregnancy, with a previous history of SC in the previous five years. The patient had a comorbidity of class I obesity. The laboratory examination results revealed an increased C-reactive protein (CRP) level, anemia, hypoalbuminemia, hypokalemia, and acidosis (pH=7.33). The chest radiograph indicated bilateral pneumonia. We diagnosed the patient with respiratory failure and treated her with oxygen supplementation using a ventilator, moxifloxacin, azithromycin, and other supportive drugs. During the insertion of the central venous catheter (CPC) on the third day of treatment, an iatrogenic pneumothorax occurred, necessitating the use of water seal drainage (WSD). On the fifth day, the patient experienced rapid deterioration, with 75% oxygen saturation while using the ventilator, a PEEP of 11, and a FiO2 of 100%. Respiratory failure occurred, and the patient eventually died. The delivery did not happen because, according to the evaluation, the baby was not yet viable. Later, it was announced that the cause of death was acute respiratory distress syndrome due to COVID-19 pneumonia.

Case 3

A 32-year-old woman, Mrs. H, was 30–31 weeks pregnant. It was her fifth pregnancy, with a history of three abortions. The patient came to the hospital complaining of coughing and shortness of breath for three days. Previously, the patient received antenatal care twice: once with obstetricians and twice at the primary health center. She was categorized as having a high-risk pregnancy because of her history of recurrent miscarriage, class II obesity, and pre-pregnancy diabetes. On arrival at our hospital, the patient had shortness of breath. The respiration rate was 30 breaths per minute while using a 6 L/min oxygen mask, and the oxygen saturation was 95%. The laboratory examination results showed an increased random blood sugar level (216 mg/dL) and CRP, while the chest radiograph showed bilateral pneumonia. In accordance with the gestational age (30 weeks) and the estimated fetal weight (1,500 g), conservative obstetric treatment was administered. The medical management included the administration of medications, i.e., oseltamivir and azithromycin, as well as injections of levemir and novorapid for blood sugar regulation and other supportive therapy. On the second day of treatment, the patient's condition worsened, with a decreased oxygen saturation of 89%. Therefore, the patient was put on a ventilator and admitted to the ICU. On the fourth day of treatment, when the mother had respiratory failure and metabolic acidosis, we decided to perform an emergency termination for maternal-fetal lifesaving. A baby boy was born through SC with a 1,615-g body weight, 36.5-cm body length, and an Apgar score of 1–1–1. Unfortunately, the baby died two hours after birth. On the seventh day of treatment, widespread pneumonia was seen on the chest radiograph. In addition, a blood culture showed infection with *Staphylococcus hominis*, so additional meropenem antibiotic therapy was administered. In the ICU, the antiviral therapy was changed to remdesivir with a dose of 200 mg daily. On the tenth day of treatment, the patient's condition continued to worsen, and further respiratory failure occurred. The oxygen saturation was 70% while using the ventilator. Later that day, the patient died. The cause of death was acute respiratory distress syndrome due to COVID-19 pneumonia, with comorbid obesity and pregestational diabetes mellitus.

Case 4

Mrs. NA, 31 years old, was 27–28 weeks pregnant and referred to the hospital with complaints of coughing, cold, and fever for two days. This was her second pregnancy with a history of SC at 27 weeks gestation. On arrival, the patient had shortness of breath with a respiration rate of 26 breaths per minute and an oxygen saturation of 98% while using an 8 L/min oxygen mask. The COVID-19 screening showed a positive antigen swab and reactive immunoglobulin G (IgG), while the chest radiograph showed bilateral pneumonia. The patient was treated using 10 L/min oxygen therapy, a non-rebreathing mask, oseltamivir, and other supportive therapy. We decided to maintain the pregnancy with conservative care according to the gestational age. On the fourth day of treatment, the condition worsened. The patient experienced respiratory failure with an oxygen saturation of 93%; thus, the patient was put on a ventilator and admitted to the ICU. During the treatment, we found decreased levels of albumin, potassium, and hemoglobin, as well as increased levels of ferritin. While using the ventilator, the patient's oxygen saturation remained low (93–95%), and intrauterine fetal death (IUFD) occurred. On the seventh day of treatment, the oxygen saturation decreased to 70%. The condition continued to worsen until the patient died. The cause of death was acute respiratory distress syndrome due to COVID-19 pneumonia.

Case 5

A 41-year-old woman, Mrs. S, was 39 weeks pregnant. This was her second pregnancy following a cesarean delivery seven years prior. The patient was referred to the hospital with complaints of coughing, spasms, a headache, nausea, and vomiting. On arrival, the patient had shortness of breath. The respiration rate was 36 breaths per minute while using a non-rebreathing mask on 10 L/min oxygen supplementation. The oxygen saturation was 55–60%. We found a blood pressure of 189/110 mmHg and a urine protein of +3. Thus, we diagnosed the patient with severe pre-eclampsia. According to the results of COVID-19 screening, we found that the IgG was reactive with bilateral pneumonia. For the initial management, we administered magnesium sulfate (MgSO4) injections, nifedipine, and methyldopa for the severe pre-eclampsia condition. In accordance with the gestational age, severe pre-eclampsia diagnosis, location of the breech, and additional COVID-19 pneumonia, we decided to perform SC for the delivery. A baby boy was born with a 2,655-g body weight, a 49-cm body length, and an Apgar score of 3-5. Uterine atony occurred during the SC procedure, and uterine compression sutures were performed unsuccessfully using the Surabaya Method (Jiang et al. 2020). Later on, a supravaginal hysterectomy (SVH) was performed. Postoperatively, the patient was admitted to the ICU and put on a PEEP of 10 on the ventilator, with an oxygen saturation of 95–99% and hemoglobin of 8.1 mg/dL. During treatment, we found that the levels of procalcitonin, D-dimer, hemoglobin, and albumin decreased. The patient received daily doses of 750 mg levofloxacin therapy and 100 mg cortisone, as well as 300 units/hour of heparin, 300 mg chloroquin twice a day, and other supportive therapy. In the ICU, the patient's condition worsened, and the oxygen saturation was unstable (80–93%). On the fifth day of treatment, the patient died. The cause of death was acute respiratory distress syndrome due to COVID-19 pneumonia with complications of severe pre-eclampsia, postpartum hemorrhage due to uterine atony, and class I comorbid obesity.

Case 6

Mrs. N, 31 years old, was referred from a rural hospital (193 km from our hospital) with chief complaints of shortness of breath. This was her second pregnancy, with a gestational age of 27–28 weeks and an estimated fetal weight of 900 g. The patient experienced coughing, a cold, and joint pain for two weeks prior to being admitted to the previous hospital. The patient was a physician and already had supportive medicines at home before coming to the previous hospital. After five days of treatment, the fever and cough worsened, and anosmia symptoms started to occur. After a week of treatment at the previous hospital, a swab was collected for a polymerase chain reaction (PCR) test, and the result was COVID-19 positive. Afterwards, the patient was referred to our hospital for further treatment. On arrival at our hospital, the patient had shortness of breath with a respiration rate of 32 breaths per minute and 91% oxygen saturation. The laboratory results revealed mild anemia, hypoalbuminemia, and elevated NLR, CRP, and D-dimer levels. The patient was then given oxygen supplementation through a high-flow nasal cannula (HFNC), daily doses of 500 mg azithromycin and 750 mg levofloxacin, twice-daily doses of 75 mg oseltamivir and 6 mg dexamethasone injections (for fetal lung maturation), and other supportive therapy. Because of the worsening symptoms, we decided to put the patient on a ventilator with a PEEP of 10 and 100% FiO2. On the fourth day of treatment, when vaginal bleeding occurred, we performed pregnancy termination by administering 100 mg of misoprostol vaginally every six hours. A baby girl was born, weighing 1,000 g and measuring 39 cm in length, with an Apgar score of 0. We also found a high interleukin-6 (IL-6) level, necessitating a 600 mg Actrema injection. During hospitalization, the symptoms worsened with a gradual decrease in oxygen saturation. On the sixth day of treatment, the patient's condition worsened with 53% oxygen saturation and blood pressure. The pulse continued to decrease despite dopamine administration. Later that day, the patient died after chest compressions were performed. The cause of death was acute respiratory distress syndrome (ARDS) due to COVID-19 pneumonia.

Case 7

Mrs. K, 31 years old, was referred to a private hospital after experiencing shortness of breath for two days, along with coughing and fever for three days. This was her first pregnancy, and she was 35 weeks pregnant without any additional complications or comorbidities. On arrival, the patient had shortness of breath with a respiration rate of 26–28 breaths per minute and 91% oxygen saturation. The blood pressure was 130/70 mmHg, and the pulse was 120 beats per minute. We found bilateral pneumonia on the chest radiograph, with 16,900 leukocytes and increased liver function, as well as elevated D-dimer (6.2 ng/mL), CRP (219.4 mg/L), and NLR (23.25) levels. The patient was given oxygen supplementation, twice-daily doses of 75 mg oseltamivir and 300 mg chloroquin, 400 units of heparin per hour, and other supportive therapy. We decided that the pregnancy would be terminated after lung maturation with twice-daily doses of 6 mg dexamethasone via intramuscular (IM) for two days. On the second day of treatment, fetal bradycardia

occurred. An emergency SC was then performed, and a baby girl was born with 2335 g of body weight, 44 cm of body length, and an Apgar score of 3–5–7. Two days after surgery, the patient's oxygen saturation dropped to 88%, so we decided to put her on a ventilator. However, the patient's condition continued to worsen. On the seventh day of treatment, the patient died. The cause of death was acute respiratory distress syndrome due to COVID-19 pneumonia.

DISCUSSION

Since March 2020 until the end of January 2021, Rumah Sakit Universitas Airlangga had delivered 108 babies related to confirmed COVID-19 infections. However, 81 highly suspect cases of COVID-19 were unable to be confirmed using reverse transcription polymerase chain reaction (RT-PCR) due to a lack of available supplies. There were seven maternal deaths from 108 cases related to COVID-19, with a case fatality rate of 6.48%. All the maternal deaths were caused by acute respiratory distress syndrome (ARDS) related to COVID-19. The maternal background, clinical symptoms, and diagnosis of the patients in this case series can be seen in Table 1. The maternal age range was 28–41 years old. Six patients were multiparous, with gestational ages of 22–40 weeks during admission. Three patients came to our hospital by themselves, while the rest were referred by other hospitals because of worsening conditions during treatment (Dewantiningrum et al. 2023).

Table 1. Maternal background, clinical symptoms, and diagnosis of the pregnant women.

	J	LH	H	NA	S	N	K
Age (years)	38	28	32	31	41	31	31
Length of stay (days)	4	5	10	8	6	8	8
ANC	Hospital 9x	Mother and Child Hospital 5x	PHC 2x, Specialists 2x	Hospital 5x	PHC 4x, Hospital 1x	Hospital 4x	PHC 5x
Referral	Referred by the previous hospital	Referred by the previous hospital	Came by herself	Came by herself	Came by herself	Referred by an out-of-town hospital	Referred by the previous hospital
Gestational age at admission (weeks)	33	22	30	27	40	27	35
Comorbidity	Class I obesity	Class I obesity	Class I obesity and pregestational diabetes mellitus	-	Class I obesity	-	-
Symptom	Fever, dyspnea, and coughing (1-2 weeks)	Coughing and dyspnea (3 days)	Coughing, dyspnea, and fever (3 days)	Fever, coughing, and flu-like symptoms (2 days)	Dyspnea, headache, and nausea	Dyspnea	Coughing, myalgia, fever, and dyspnea (4 days)
Blood pressure (mmHg)	101/68	128/64	117/63	113/74	189/110	109/61	130/70
Respiratory rate (breaths/minute)	32	32	30	26	36	32	28
Temperature (ºC)	36.7	37.7	36	36.5	36.4	36.8	37.8
Oxygen saturation during admission (%)	60% in a free O_2 room, 96% with 15 L/min of O_2 using NRM	77% in a free O_2 room, 90% with 12 L/min of O_2 using NRM	95% with 6 L/min of O_2 using a simple mask	98-99% with 8 L/min of O_2 using a simple mask	55-60% with 10 L/min of O_2 using NRM	90% with 10 L/min of O_2 using NRM	92% with 10 L/min of O_2 using NRM
Rapid antibody test	(+)	N/A	(+)	(+)	(+)	(+)	(+)
Rapid antigen test	N/A	N/A	N/A	(+)	N/A	N/A	(+)
Chest X-ray	Bilateral pneumonia	Bilateral pneumonia	Bilateral pneumonia	Bilateral pneumonia	Bilateral pneumonia	Bilateral pneumonia	Bilateral pneumonia

PHC: Primary health center. NRM: Non-rebreathing mask. N/A: Not available.

Six patients came with the chief complaint of dyspnea, a respiratory rate of 26–36 breaths/minute, and oxygen saturation in free roam between 50–95%. There were only two patients with fevers (t>37.5°C) during admission. Symptoms of shortness of breath and fever indicate the presence of COVID-19 pneumonia, which seems to be an indicator that COVID-19 will be severe or critical. According to a study, fever (40%), cough (39%), and shortness of breath (19%) were the most common clinical manifestations seen in pregnant women with COVID-19 infection. However, the likelihood of fever in pregnant women is lower than in non-pregnant women infected with COVID-19 (OR=0.43) (Allotey et al. 2020, Villar et al. 2021; Atmaja et al. 2022). In this case series, all patients experienced symptoms within 2–4 days. As for Mrs. J, the patient had the symptoms for 1–2 weeks, which might indicate a delay in the COVID-19 diagnosis, treatment, and therapy (Table 1). According to our analysis, the root cause might be that all cases in this study happened at the beginning of the pandemic, thus indicating that neither the patients nor medical personnel had a high suspicion of COVID-19.

Six patients had positive results from the rapid antibody tests, and all cases had bilateral pneumonia on chest X-ray imaging. At the beginning of the pandemic, we used serological antibody tests to screen for COVID-19, given the limitations of PCR testing at our center. A combination of clinical symptoms, laboratory tests, chest X-rays, and rapid antibody tests may detect the majority of COVID-19 cases at our hospital (Laksana et al. 2020, Wardhana et al. 2021, Akbar et al. 2023). However, due to its limited sensitivity and specificity, the serologic antibody test as a screening method has now been replaced by the antigen swab test. The presence of pneumonia is considered a more sensitive indicator of COVID-19, as the sensitivity of a chest CT scan may exceed that of an RT-PCR swab examination in the early phase of infection (Rashid et al. 2020, Porte et al. 2020, Mair et al. 2021).

The clinical management and pregnancy outcomes are summarized in Table 2. The patients were treated mainly with antivirals, antibiotics, and anticoagulants based on their personal conditions, in addition to supportive therapy. According to the COVID-19 guidelines, therapies that should be given were still very diverse, and the management of COVID-19 in pregnancy at our hospital also varied depending on the patient's condition (Laksana et al. 2020). In this study, five patients received oseltamivir as their antiviral therapy. Oseltamivir is a neuraminidase inhibitor that is widely used for influenza A and B therapy. The structure of the spike S1 protein in SARS-CoV-2 resembles that of neuraminidase. Therefore, neuraminidase inhibitor drugs, such as oseltamivir, can be useful in SARS-CoV-2 therapy. In silico, in vitro, and clinical studies by Tan et al. (2020) in Wuhan, China, showed that oseltamivir was ineffective in the therapy of COVID-19. From the total of 79 COVID-19 patients that used oseltamivir, remission was found in only 22.58% of the patients, a number much smaller than the non-remission cases at 72.9%

Table 2. Clinical management and pregnancy outcomes of the hospitalized patients.

	J	LH	H	NA	S	N	K
Antivirals	Oseltamivir, 2 x 75 mg	(-)	Oseltamivir, 1 x 75 mg	Oseltamivir, 2 x 75 mg	(-)	Oseltamivir, 2x 75 mg	Oseltamivir, 2x 75 mg
Antibiotics	Levofloxacin, 1 x 750 mg	Moxifloxacin, 1 x 400 mg	Meropenem, 3 x 1 g	(-)	Levofloxacin, 1 x 750 mg	Moxifloxacin, 1 x 400 mg	Meropenem, 3 x 1 g
Anticoagulants	Heparin, 350 units/hour	(-)	Heparin, 300 units/hour	(-)	(-)	Heparin, 500 units/hour	Heparin, 400 units/hour
Delivery	SC	not delivered	SC + IUD	not delivered	SC	Labor induction using misoprostol	SC
Delivery Complications	(-)	(-)	(-)	(-)	Uterine atony, SVH due to failed conservative surgery	(-)	(-)
Newborn	Girl, 1,960 g, 46 cm, AS: 7–8, survived	IUFD, not delivered	Boy, 1,615 g, 36.5 cm, AS: 1–1–1, death in hours	IUFD, not delivered	Boy, 2,655 g, 49 cm, AS 3–5, survived	IUFD: Girl, 1,000 g, 39 cm, AS 0	Girl, 2,335 g, 44 cm, AS 3–5–7, survived
Admission to ICU	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Ventilator	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Length of ICU stay (days)	3	4	8	5	5	7	4

($p<0.001$). On the other hand, prolonged oseltamivir therapy did not improve the patient's condition. In our hospital, oseltamivir was used at the beginning of the pandemic because of its availability and theoretical background. However, after many reports about the ineffectiveness of this drug and the entry of various new drugs, the use of oseltamivir for COVID-19 therapy was replaced by remdesivir (Beigel et al. 2020).

Antibiotics are not routinely given in COVID-19 cases. The medications are only administered in COVID-19 cases with superimposed infections, particularly bacterial pneumonia. The antibiotics used in our cases were meropenem, levofloxacin, and moxifloxacin. Currently, the antibiotics recommended for treating bacterial pneumonia in pregnant women are from the macrolide group and may be added with beta-lactam in severe disease conditions (Nasrallah et al. 2022). Both of the drugs have good safety profiles in pregnancy (FDA class B). Meropenem is a broad-spectrum beta-lactam antibiotic used in severe infections. In this study, there were two patients who received meropenem antibiotic therapy. Meanwhile, four other patients received therapy with antibiotics from the fluoroquinolone class. The fluoroquinolone class of antibiotics is highly effective against bacterial pneumonia. Fluoroquinolones have a bactericidal effect by inhibiting DNA synthesis and interacting with DNA gyrase and topoisomerase IV in cells. However, the use of fluoroquinolones raises concerns about their safety in pregnancy. Current clinical data indicate that the fluoroquinolone class is relatively safe to use in pregnancy and poses a low risk (Yefet et al. 2014). The FDA categorizes this class of drugs into category C, which means the benefits of administration outweigh the risks, and it

Table 3. The maternal laboratory results from all cases.

	J	LH	H	NA	S	N	K
Hb (mg/dL)	10.7*	11.4	12.7	10.4*	13.7	9.5*	11.3
Leukocyte (x 10^9/L)	10.52	15.91*	2.97*	6.9	26.6*	7.01	16.9*
Thrombocyte (x 10^9/L)	228	241	252	159	391	268	287
Hematocrit (%)	32.4	32.9	36.3	31.9	41.2	28	33.8
NLR	6.16	N/A	2.82	N/A	1.74	6.67	23.25
Random blood glucose (mg/dL)	109	120	216*	N/A	N/A	219*	N/A
BUN (mg/dL)	5.1	3.2	5.3	5.2	10	4.2	13.6
Serum creatinine (mg/dL)	0.18	0.27	0.67	0.41	0.53	0.49	1.18
Albumin (g/dL)	N/A	2.19*	3.16*	3.1*	3.26*	3.05*	2.8*
ALT (U/L)	N/A	64*	68*	33	21	44*	215*
AST (U/L)	N/A	42	34	19	10	44	215*
Natrium (mEq/L)	138	132*	135	137	140	135	130*
Kalium (mmol/L)	3.5*	3.1*	4.3	3.2*	4.6	3.6*	4.9
Chloride (mEq/L)	108	109	108	110	111	111	105
PPT (seconds)	N/A	10	11.1	12.6	11.4	11.8	N/A
APTT (seconds)	N/A	27	26.6	34.3	32.8	35.1	N/A
Procalcitonin (ng/mL)	N/A	0.15	0.41	0.3	2.78*	0.24	1.45
CRP (mg/L)	N/A	114.2*	68.86*	64.61*	N/A	78.47*	219.4*
Ferritin (mcg/L)	N/A	128.7	N/A	415	N/A	309.5	N/A
IL-6 (pg/mL)	N/A	N/A	44.67*	N/A	N/A	75.77*	N/A
D-dimer (µg/mL)	2.9*	9.75*	1.1*	2.59*	8.29*	1.28*	6.2*

BUN: Blood urea nitrogen; ALT: Alanine transaminase; AST: Aspartate aminotransferase; PTT: Partial thromboplastin time; APTT: Activated partial thromboplastin time.

Table 4. Daily monitoring of oxygen saturation in all cases (%).

	Admission	D+1	D+2	D+3	D+4	D+5	D+6	D+7	D+8	D+9	D+10
J	97	93	100	70							
LH	100	95	94	95	70						
H	95	98	89	100	99	93	98	98	97	97	70
NA	98	96	96	93	95	94	87	70			
S	55	93	90	86	92	85	81				
N	90	83	99	97	96	90	82	70	53		
K	91	92	90	85	100	98	92	83	78		

Notes: Green: Using simple oxygen mask. Blue: Using non-rebreathing oxygen face mask. Yellow: Using ventilator. Red: Maternal death.

may be used in pregnancy.

All patients in this study had elevated D-Dimer levels (>0.5 µg/mL), indicating a poor prognostic in patients with COVID-19. Unfortunately, not all patients received anticoagulant therapy (heparin). The reason was that all cases occurred at the beginning of the pandemic, when the guidelines for the management of patients with COVID-19, especially in pregnancy, were not yet established. As of now, we know that COVID-19 causes hypercoagulability, and the cytokine storm will cause abnormal clot formation and platelet hyperactivation (Miesbach & Makris 2020). Tang et al. (2020) reported that elevated D-dimer levels in COVID-19 patients were a predictor of mortality. In their study, mean D-dimer levels were found to be higher in the group who died than in the survivors of COVID-19 (2.12 vs. 0.61 µg/mL). Another study showed that elevated D-dimer levels (>1 µg/mL) increased the risk of death in COVID-19 patients (OR=18.4; 95% CI=2.6–128) (Zhou et al. 2020).

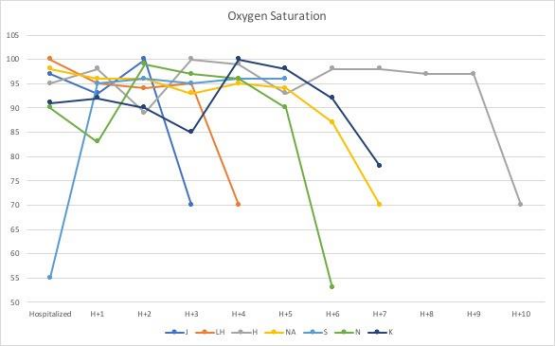

Figure 1. Progression of oxygen saturation during treatment.

Four patients delivered their babies by SC, and one patient delivered vaginally with misoprostol induction. Two patients were unable to deliver, i.e., Mrs. LH due to unviable gestational age (22 weeks) when maternal deterioration occurred and Mrs. NA due to the rapid worsening of the maternal condition. There is no evidence from scientific studies to suggest that one method of delivery is superior to another. In three out of four cases, the indication for SC was deteriorating COVID-19 symptoms, and ventilators were required during the procedure. The purpose of SC is to improve the condition of the mother by reducing the physiological burden of pregnancy. Obesity was found to be one of the risk factors for pre-eclampsia (Kartika et al. 2018). In the case of Mrs. S, SC was performed because of severe pre-eclampsia indications, gestational age, and the location of the breech. There were only three babies that survived from the total of seven cases (42.8%). This happened despite a previous study stating that all pregnancies with COVID-19 infections have a low perinatal mortality rate (2 of 108) (Pacheco et al. 2020, Zaigham & Andersson 2020). In cases of pregnancy with severe COVID-19 manifestations, the perinatal mortality rate appears to increase significantly. The cause of death in these conditions is chronic uteroplacental insufficiency or hypoxia due to prolonged maternal hypoxia, accompanied by prematurity. All infants who died were born at <32 weeks gestation.

The results from the laboratory tests during admission can be seen in Table 3. Almost all patients in these cases suffered from multiple organ dysfunctions, which were visible in the laboratory results. Only renal functions did not show any abnormalities in all cases. The CRP, IL-6, and D-Dimer levels significantly increased, although these markers were not always examined in all cases. Table 4 demonstrates the oxygen saturation progression day by day. Three methods were used as respiratory support, i.e., simple masks, non-rebreathing masks (NRM), and ventilators. On average, the patients experienced respiratory deterioration from days 2–4 before death. The exceptions were Mrs. L and Mrs. S, who suffered very fast respiratory failure on the day of the death. Oxygenation support is one of the most important factors in treating COVID-19 patients. Pregnant women require a higher minimum oxygen saturation level than non-pregnant women due to the increase in oxygen demand and oxygen partial pressure that occurs during pregnancy. In the care of pregnant women with COVID-19, oxygenation must be maintained with a minimum oxygen saturation of 96%. In this study's cases, the use of ventilators failed to reach the expected oxygen saturation minimum target. This indicated that severe lung damage and respiratory failure caused by COVID-19 might eventually become the leading cause of death in all cases (Dewantiningrum et al. 2023).

Strength and limitations

This case series illustrates the severe clinical progression of COVID-19 in pregnant women during the earliest phases of the pandemic, when all pregnant women had not yet been vaccinated against COVID-19. The strength of this case series is that it accurately reflects the natural clinical progression of COVID-19 during pregnancy in the absence of vaccination. These cases demonstrate that pregnancy is a major risk factor for severe and fatal COVID-19 infections. After the government initiated a vaccination program, maternal mortality and morbidity caused by COVID-19 decreased significantly. This highlights the significance of vaccination for expectant women. In these cases, we can also learn about the antibiotic, antiviral, and anticoagulant treatments administered during the

initial phase of the pandemic. Access to mechanical support in a timely manner is crucial for increasing the survival rate of expectant women suffering respiratory distress due to the COVID-19 infection. Although the use of retrospective data placed limitations on this study, the information can be obtained completely from the medical records.

CONCLUSION

This study provided evidence of the significant risks posed by COVID-19 during pregnancy, particularly for unvaccinated women. The rapid progression of the disease can lead to acute respiratory distress syndrome due to severe pneumonia, which requires mechanical ventilation. In addition, severe manifestations of COVID-19 can have adverse effects on perinatal outcomes, including stillbirth and fetal growth restriction. In order to mitigate the severe clinical manifestations of COVID-19, vaccination is crucial for pregnant women.

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Conflict of interest

None.

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Author contribution

MIAA was responsible for the design of the study, the acquisition, analysis, and interpretation of the data, the drafting and revision of the manuscript, the final approval of the manuscript, and all aspects of the work related to the accuracy and integrity of any part of the work. PM was responsible for the acquisition of the data, revision, and final approval of the manuscripts. MPW was responsible for the acquisition and analysis of the data, as well as the final approval of the manuscript. KEG and E were responsible for the acquisition, analysis, and interpretation of the data, as well as the revision and final approval of the manuscript. ER, MACL, and JYA were responsible for the acquisition of the data, revision, and final approval of the manuscript. HTJ, MAB, and BAT were responsible for the revision and final approval of the manuscript.

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