



Pregnant Women Infected with Coronavirus Disease 2019 Pneumonia: A Case Series in Medan, Indonesia

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Abstract

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BACKGROUND: Pregnancy state affects the immune regulation including physical barrier, innate, and adaptive immunity-related to susceptibility of infections and increasing risk for severe to critical case of COVID-19. Further, high risk of thrombosis becomes a challenge in the management of COVID19 in pregnancy due to the strong association with worse outcome.

CASE REPORT: Here, we present three cases of pregnant women infected with COVID-19 pneumonia with different outcomes in maternal and fetal condition related to high-risk thrombosis. Serial inflammatory markers were needed to the early detect the disease progressivity in pregnant women with COVID-19. Further, complete assessment of fetus including reverse transcriptase-polymerase chain reaction and chest X-ray must be performed to the early diagnosis of COVID-19 in neonatal whose mother was infected by SARS-CoV-2.

CONCLUSION: Pregnancy state affects the immune regulation including physical barrier, innate, and adaptive immunity-related to susceptibility of infections and increasing risk for severe to critical case of COVID-19. Further, high risk of thrombosis becomes a challenge in the management of COVID19 in pregnancy due to the strong association with worse outcome. Although fetal transmission of COVID-19 to fetus remains unclear, complete assessment of fetus including RT-PCR, and chest X-ray must be performed to the early diagnosis of COVID-19 in neonatal whose mother was infected by SARS-CoV-2.

Introduction

Viral pneumonia, particularly COVID-19 infection, rises adverse impacts on maternal and neonatal outcomes. A recent study showed that pregnant women have a higher risk for hospitalization and the use of mechanical ventilation compares with non-pregnant women [1]. Furthermore, the increase of circulating coagulation and fibrinolytic factors in pregnancy worsens the hypercoagulable state, resulted in a cytokine storm in COVID-19 [1]. All these factors affect the systemic inflammation and circulatory disorder that give additional worse impact in patients [1], [2].

Here, we present three cases of COVID-19 infection in our region with different clinical characteristics and outcomes.

Case Reports

Case 1

A 33-year-old pregnant woman, gravida 2, with 39–40 weeks' gestation admitted to the hospital with the

chief complaint was taste disturbance and loss of sense of smell without any respiratory complaints. There was no history of comorbidities. She was prepared for a section cesarean (SC) procedure and showed positive results reverse transcriptase-polymerase chain reaction (RT-PCR) test. At present, physical examination was normal. Chest X-ray on August 25, 2020 remained normal with no sign of pneumonia (Figure 1). Laboratory findings were normal white blood counts (WBC) with a mild increase of neutrophil, normal PaO₂/FiO₂ fraction, increased D-dimer, and fibrinogen, normal C-reactive protein (CRP), procalcitonin (PCT), and ferritin. There was no increase in cardiac and liver enzymes (Table 1). Electrocardiography (ECG) was under normal condition. On August 26, 2020 at 11.00 am, the SC procedure was performed without any significant difficulties. After 2 h in the isolation recovery room, she was discharged with an Aldrete score of 9. 4 h later, she was suddenly felt limp and shortness of breath. Her vital sign was deterioration with blood pressure (BP) 70/palpable, heart rate (HR) 100 times/min, respiratory rate (RR) 20 times/min, and 50% oxygen saturation. High flow oxygen with positive pressure was given for 10 min, but there was no clinical improvement. In 1 h, the clinical conditions became worsen and she was apnea with ECG showed Asystole. Cardiopulmonary Resuscitation



Figure 1: Chest X-ray of 33-year-old women gravida 2, with 39–40 weeks' gestation diagnosed with confirmed case of COVID-19 with mild symptom. There was no sign of pneumonia and cardiomegaly.

was performed with injection of epinephrine, but there was no clinical improvement. She was declared dead at 07.20 pm, after 30 min of CPR. The autopsy procedure was not performed due to refusal from the patient's family, so the exact mechanism of death was still unclear. However, pulmonary thromboembolism was the most probable cause of death in this case.

Her baby was in normal condition with normal blood parameters with negative results in RT-PCR test.

Table 1: Clinical information about pregnant women with coronavirus disease-2019 in first admission in Universitas Sumatera Utara Hospital, Indonesia

Characteristics	Case 1	Case 2	Case 3
Hb (g/dL)	11.6	8.7	10.8
WBC (10 ³ /uL)	10.180	9.60	8.70
PLT (10 ³ /uL)	282	256	525
Neutrophil (%)	67.3	73.5	74
Lymphocyte (%)	23.6	18	16.3
Ferritin (ng/mL)	1860	7.86	>2000
PT (s)	12.5	11.9	12.7
APTT (s)	29.3	27.3	27.6
TT (s)	16.5	16.1	17.2
D-dimer (ug/dL)	1501	6446	4000
Ureum (mg/dL)	12.6	9.7	35.6
Creatinine (mg/dL)	0.61	0.56	0.86
Natrium (mmol/L)	136	141	138
Kalium (mmol/L)	4.26	3.75	4.12
Chloride (mmol/L)	102	105	103
AST (U/L)	28	28	32
ALT (U/L)	25	24	28
pH	7.42	7.42	7.38
pCO ₂ (mmHg)	31.7	32.7	30.2
pO ₂ (mmHg)	165.7	179.4	134.3
HCO ₃ ⁻ (mmol/L)	20.6	20.9	23.4
SaO ₂ (mmol/L)	98	99	99
CRP quantitative (mg/dL)	1.7	1.9	2.8
Procalcitonin (ng/mL)	0.08	0.08	0.03
Fibrinogen (mg/dL)	742	460	857
Troponin T	17	15	19

Hb: Hemoglobin, WBC: White blood counts, PLT: Platelet, PT: Prothrombin time, APTT: Activated partial thromboplastin time, AST: Aspartate aminotransferase, ALT: Alanine transaminase, CRP: C-reactive protein.

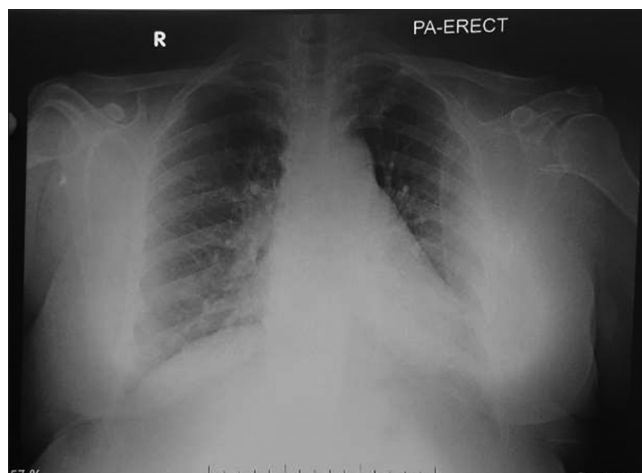


Figure 2: Chest X-ray of 26-year-old women gravida 1, with 35–36 weeks' gestation diagnosed with confirmed case of COVID-19 with moderate symptoms. Bilateral infiltrations with cardiomegaly were seen.

Case 2

A 26-year-old pregnant woman, gravida 1, with 35–36 weeks' gestation admitted to hospital with the chief complaint was bloody discharged 2 days before admitted to the hospital. Bloody discharged was not followed by any contractions. Cough was experienced intermittently without sputum productions for 7 days. Other respiratory symptoms were not present. At present, oxygen saturation was 90% room air and remained 94% after 5 L/min (l pm) of oxygen nasal cannula with stable BP. Chest X-ray revealed a bilateral infiltration (Figure 2) with positive RT-PCR Test. Laboratory examination showed mild anemia and slight decrease in lymphocyte percentage, increase of D-dimer, mildly increased PCT, with normal CRP (Table 1). Vitamin K and tranexamic acid were administrated to control the vaginal bleeding. Tocolytic was given to decrease the uterine contraction. Other medications administrated were symptomatic drugs

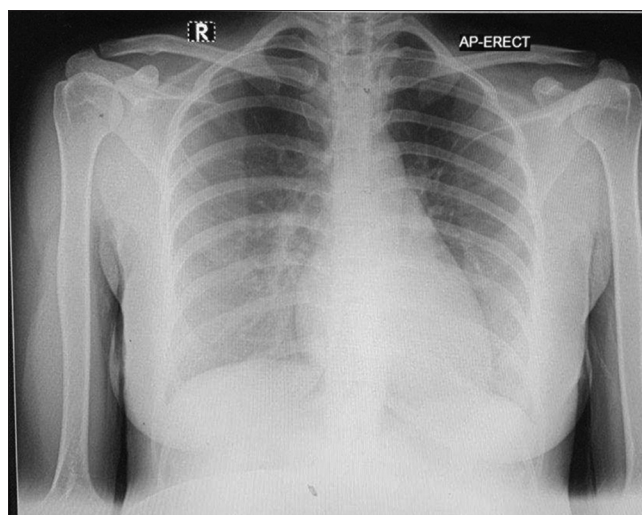


Figure 3: Chest X-ray of 32-year-old women gravida 2, with 39–40 weeks' gestation diagnosed with confirmed case of COVID-19 with moderate symptoms. Bronchopneumonia appearance was seen with no sign of cardiac abnormality.

and vitamin. After administration of 0.4 cc Enoxaparin, vaginal bleeding becomes more severe. Hence, we stop the anticoagulant drug. There were no progressive respiratory symptoms for three weeks of hospitalization, but the D-dimer remained over 3000 ng/mL. Vaginal bleeding still occurred in mild grade and after 37 weeks of gestation, SC was carried out without any complication. She was discharged 3 days after SC with no clinical symptoms, but the RT-PCR swab remained positive for 42 days.

The baby was under the normal condition with negative results of RT-PCR. There was no sign of infections, although the blood examination showed mild leukocytosis.

Case 3

A 32-year-old pregnant woman, second gravida with gestation 39–40 weeks admitted to hospital with the chief complaint, was abdominal pain in the past 6 h before admitted to the hospital. Fever was found in 3 days before admitted to hospital. Other viral illness was not found. Physical examination was under normal limit, but the oxygen saturation was constant in 95–96% room air. There was no sign of respiratory distress. She was scheduled for section cesarean and undergone blood routine and chest X-ray. Chest X-ray revealed bilateral infiltration (Figure 3), but the rapid test for antibody of SARS-CoV2 showed negative, yet the RT-PCR revealed positive. Laboratory showed mild anemia, thrombocytosis, and increased of D-dimer. After 7 days of course of disease, shortness of breath was developed with marked increase of hemostatic parameters. Doses of anti-coagulant was increased, and restricted monitoring of hemostatic parameters was performed in case of bleeding tendency after SC procedure. Leukocytosis was occurred after 12 h of SC and antibiotics including meropenem and levofloxacin were administered. Methylprednisolone 62.5 mg for 12 h was administered to decrease hyperinflammation state. Ten days after extensively antibiotics and steroid, patient's condition improved with normal leucocyte count and reduced D-dimer < 1000. The patient was discharged after follow-up RT-PCR showed negative results.

After birth, the baby was tested RT-PCR for COVID-19 and showed positive results. Laboratory and Chest X-ray was under normal limit with no significant clinical examination. The baby was discharged after 10 days of hospitalized.

Discussion

Physiological response in pregnancy affects the immune system and led pregnant women vulnerable to COVID-19 infection [2]. All these presented cases

were in mild-to-moderate symptoms when admitted to the hospital and for case number 2 and 3, patients remained stable until discharge from the hospital. However, for the first case, sudden deterioration of conditions occurred after SC and caused maternal death. The difference of outcome in COVID-19 is affected by multifactorial including pre-existing disease [3], nutrition, and mental state. For the asymptomatic and mild disease, the modulation of the immune system was enough to control inflammatory results in the reaction toward SARS-CoV-2 viruses and physiological change in pregnancy state [2]. Expression of T-helper 1 associated CD4+ enhanced neutralized antibody to blocked virus replication, then the macrophage engulfed the infected cells [4]. However, in pregnant women with comorbidities, such as age >40 years old, cardiovascular disease, kidney disease, diabetes mellitus, and dyslipidemia, there are several changes in immune response which played important role in the severity of cytokine storm in inflammatory state condition [5], [6], [7]. Whereas in our cases, all patients have no comorbidities. Hence, the disease progressivity in the first case might be caused by psychological and physiological stress after SC. Unfortunately, we did not perform serial chest X-Ray before and after the patient was undergoing the SC procedure. Complete blood count showed mild leukocytosis (11.550 cells/uL) without any substantial difference from baseline. Arterial blood gases also showed respiratory alkalosis without any sign of sudden respiratory hypoxemia.

Acute pulmonary thromboembolism is the major causal of death in COVID-19 infection, followed by myocarditis, acute coronary disease, hypoxia, high-grade inflammatory state, cardiac tamponade, electrolyte imbalance, and arrhythmia [8], [9]. Few factors induce the hypercoagulable state in pregnancy. First, physiological response in pregnancy synergistic escalating the hypercoagulable state by increasing the thrombin production, circulating coagulation and fibrinolytic factor, and enhancing intravascular inflammations [6], [10]. Furthermore, the SARS-CoV-2 virus itself was able to activate the coagulation cascade [7]. Hence, the thromboprophylaxis was needed for preventing the acute thrombopulmonary event that will give worsen outcome in COVID-19 patient, although, in some cases, many considerations were carried out due to bleeding side effect like in Case 2. Good teamwork among internist, pulmonologist, and obstetrician was substantial to make decisions in giving the dose and intermittently stopping of thromboprophylaxis drug.

Different from other infections, the Disseminated Intravascular Coagulopathy (DIC) event in COVID-19 was reported in a low percentage. Local intravascular coagulopathy resulted from seriously alveolar inflammation was more familiar in COVID-19 infection [11]. In few recent review, articles showed that coagulopathy-related COVID-19 was more concentrated in pulmonic rather than systemic coagulations dysfunctions [12], [13], [14].

A study also specified termed pulmonary intravascular coagulations as the concern manifestations of COVID-19 particularly in severe disease [14]. In our cases, the D-dimer was 1500 $\mu\text{L/dL}$ with a normal fibrinogen level.

We did not administer any anticoagulant drugs such as enoxaparin, because the patient was scheduled to carry out SC procedure for the next day. There was no repeated hemostatic parameter after the procedure until the clinical condition was worsening. A recent study also stated that Venous Thromboembolism incidence highest in the postpartum period, particularly in patients with obstetric complications. This is due to higher inflammatory cytokine and tissue damage in the delivery process. Hence, the clinicians must be aware of the worsening of hypercoagulable state soon after birth, especially in COVID-19 infection [15], [16], [17], [18]. In another case, Del Nonno *et al.* reported a case about 61-year-old woman diagnosed with an asymptomatic COVID-19 infection and after 32 days, she was referred to ER with cardiac arrest. She has been tested negative for the SARS-CoV-2 virus for repeated RT-PCR test. However, her autopsy revealed bilateral pulmonary thromboembolism with edema and inflammatory alveolus [19]. This case gave the possibility of thromboembolism development and silent cytokine storm in mild disease of COVID-19. Hence, the prophylaxis of anticoagulant must be administered in every patient who has no contraindication for anticoagulant. Further, serial inflammatory markers including CRP, IL-6, fibrinogen, and TNF- α were needed to detect the early sign of disease progressivity.

Maternal death in COVID-19 infection majority occurred after delivery. Based on a recent case series, four of seven patients with severe symptoms were dead after 1–3 days after the SC procedure. In admission in ER, the hemodynamic was stable with the chief complaint that was fever, but the oxygen saturation remained below 80%. Three patients could survive more than 14 days with mechanical ventilation and the administration of double antivirus, intravenous immunoglobulin, and aggressive anticoagulant administration [20]. Five from seven patients had comorbidities including age >35-year-old, underweight, diabetes mellitus, obesity, and hypothyroid. This is different from our case who had no comorbidities. Many factors lead to the worse prognosis of COVID-19 in pregnancy, including maternal age, comorbidities, high body weight index, and non-white ethnics [16]. Yet, a systematic review and meta-analysis also reported the same cases where the patients were still younger age (25–35 years old) with no comorbidities had progressivity in their 2nd week of disease and death in 3rd trimester or after giving birth [21]. In our case, there were no factors mentioned above, so the causal of death remains unknown. Furthermore, the patient's relatives refused to do an autopsy for confirm whether

thromboembolic event after SC procedure. Further, examination in every pregnant woman with COVID-19 infection must be performed for the early detection of undiagnosed preceding disease [2].

In Case 3, a mother with mild symptoms of COVID-19 delivered the baby with positive results of RT-PCR for SARS-CoV-2. The vertical transmission of COVID-19 has been discussed in few studies [2], [3], [18], [22], [23]. In the early COVID-19 pandemic, few studies showed that there was no proof of vertical transmission of COVID-19 showed by negativity results of RT-PCR in neonates, vaginal secretion, and umbilical cord [17], [24], [25], [26]. However, a few months later, Dong *et al.* study revealed the elevated IgM antibody in neonates with a confirmed case of COVID-19 [27]. The large molecule of IgM prevents the vertical transmission across the placenta [28]. In addition, if the perinatal infection was suggested, the IgM will not be detected before 1 week after birth [29]. Hence, the presents of IgM in neonates confirm the vertical transmission of COVID-19. Another study revealed that the incidence of neonate diagnosed with confirmed case of COVID-19 was about 3% [30]. This study was review studies involved 27 studies in Asia, United States, and Europe and showed 4 of 137 neonates who birth from mother with positive SARS-CoV-2 confirmed positive in RT-PCR swab [31]. In our cases, one of three cases showed positive results in the PCR swab of the baby 1 day after birth. Vertical transmission might occur with unknown pathophysiology. In this case, we did not perform the serology test due to low sensitivity [32].

The limitations of this study are lacking umbilical cord analysis, amniotic fluid, and breast milk analysis for confirming the vertical transmission to the fetus. Despite all the limitation, this is the first international publication from our area that describes the maternal clinical course and fetal outcome in COVID-19 with pregnancy, related to increasing hypercoagulable factors.

Conclusions

Pregnancy state affects the immune regulation including physical barrier, innate, and adaptive immunity-related to susceptibility of infections and increasing risk for severe to critical case of COVID-19. Further, high risk of thrombosis becomes a challenge in the management of COVID-19 in pregnancy due to the strong association with worse outcome. Although fetal transmission of COVID-19 to fetus remains unclear, complete assessment of fetus including RT-PCR, and chest X-ray must be performed to the early diagnosis of COVID-19 in neonatal whose mother was infected by SARS-CoV-2.

Author Contribution Statement

Bintang Yinke Magdalena Sinaga is the doctor in charge of these patients and has made substantial contributions to collecting, analyzing, contributing data, and writing the article. Fannie Rizki Ananda oversees collecting data, drafting, and writing the article.

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