Case Report

Management of Severe Preeclampsia with Anemia in Pregnant Women with Covid-19 Infection : A Multidisciplinary Approach

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Abstract

Objectives: to explain the management of severe preeclampsia accompanied by anemia in pregnant women with Covid-19 Infection.

Methods: This study is a case study. The data collection process uses medical records obtained from dr. Soebandi Hospital. The data will be presented in the form of a description of the management of severe preeclampsia accompanied by anemia in pregnant women with COVID-19 Infection.

Result: In this study, we report a case of COVID-19 in a 31-year-old pregnant woman at 30-31 weeks of gestation, who is pregnant with her second child and complained of leaking amniotic fluid and shortness of breath. Physical examination results showed : positive SARS-CoV-2 antigen swab test, BP 156/112 mmHg, T (36.0°C), heart rate 107 beats per minute, respiratory rate 30 breaths per minute, fetal heart rate 144 beats per minute, SpO2 97%, urine protein +4, Hb 5.2 g%. Vaginal toucher examination revealed cervical dilation of 1 cm, negative for amniotic fluid leakage, and cephalic presentation. A spontaneous delivery occurred. A female baby was born with an APGAR score of 1-2, weighing 900 grams, a leght of 27 cm, and a normal anus. Accompanying complication include pneumonia, metabolic acidosis, anemia, melena and coagulopathy.

Conclusion: Abnormal laboratory results in pregnant women with COVID-19 can indicate the severity of the condition. So, body immunity is very important to support pregnancy and fetal growth. When the body's protection is low, the body's immunity will weaken.

Keywords: Anemia, Covid-19, Pregnancy, Severe Pre-eclampsia.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), or commonly known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), is a virus that has spread almost worldwide. COVID-19 first emerged in Indonesia on March 2, 2020, rapidly spreading throughout the country, capable of infecting the entire population, especially vulnerable groups. Pregnant women are a vulnerable group to experience health disorders, particularly infectious diseases, due to changes in their body's physiology and immune response mechanisms[1]. SARS-CoV-2 infection during pregnancy stimulates increased expression of proinflammatory cytokines such as IL-6, IL-12, IL-1β, and IFNγ, which can damage the lungs. The dominance shift to Th2 responses allows anti-inflammatory cytokines to counterbalance the expression of proinflammatory cytokines [1] , such as IL-6, which has been shown to cause severity and death in COVID-19 patients. This is why the severity of COVID-19 in pregnant women tends to be lower [2].

Anemia and Severe Pre-Eclampsia (PEB) during pregnancy can increase the risk of Covid-19 infection. Laboratory examination results of pregnant women with anemia indicate that SARS-CoV-2 infection can worsen the condition of anemia. Findings show that Covid-19 infection in pregnant women with anemia can decrease red blood cell count, hemoglobin, ferritin, serum iron, transferrin saturation, and reticulocyte count, while increasing white blood cell count and

haptoglobin levels [3]. Covid-19 infection can also trigger the occurrence of Pre-Eclampsia during pregnancy. During pregnancy, the physiological expression of angiotensin-converting enzyme-2 (ACE-2) receptors increases, particularly at placental sites. Whereas coronaviruses can bind to ACE-2 to enter human cells, causing dysregulation of the renin-angiotensin-aldosterone system and altering the ratio between angiotensin-II and angiotensin-1-7, leading to manifestations that may predispose to preeclampsia. Furthermore, cytokine storms cause endothelial dysfunction, vasculopathy, and thrombus formation, which also occur in preeclampsia [4].

Laboratory tests such as hematological examinations play a crucial role as a screening tool for patients potentially progressing towards COVID-19. Hematological changes, such as in leukocytes (lymphocytes, eosinophils, neutrophils), can depict infectious processes or indicate the severity level of infection [5]. In this study, we will report a case of Covid-19 in a pregnant woman with Severe Pre-Eclampsia (PEB) and Anemia. PEB and Anemia are pregnancy complications that may be experienced by every pregnant woman, and these conditions can be exacerbated when the pregnant woman is infected with Covid-19. This case report will provide clinical information related to pregnancy cases with Covid-19 and the accompanying complications. The aim of this study is to identify the clinical symptoms experienced by pregnant women with Severe Pre-Eclampsia and the complications associated with pregnant women infected with Covid-19.

CASE DESCRIPTION

A 31-year-old woman, pregnant with her second child, presents with Severe Pre-Eclampsia (PEB) and Anemia. The patient arrived at the hospital accompanied by a midwife, complaining of shortness of breath and leaking amniotic fluid. The midwife's examination already showed cervical dilation (1 cm). Upon arrival at the hospital, a swab antigen test was performed and returned positive for SARS-CoV-2. The patient had been attending regular antenatal visits. In terms of medical history, the patient reported no previous underlying health conditions.

Physical examination revealed high blood pressure (abnormal), tachycardia (heart rate 107 beats per minute), and abnormal breathing (signs of respiratory distress). Initial examinations included a complete blood count and blood biochemistry panel. The results showed leukocytosis, lymphopenia, and abnormal hematocrit levels.

The patient received collaborative care between an obstetrician and an internal medicine specialist. Based on the consultation with the obstetrician, the patient was advised to undergo hemodialysis and receive $MgSO_4$ therapy. Meanwhile, based on the consultation with the internal medicine specialist, the patient was advised to receive cefuroxime and remdesivir treatment.

The delivery process was spontaneous. A female baby was born, with an APGAR (AS) of 1-2, weighing 900 grams, length of 27 cm and confirmed to have an anus.

RESULTS

Physical examination results revealed blood pressure of 156/112 mmHg, temperature (38.0°C), heart rate of 107 beats per minute, respiratory rate of 30 breaths per minute, SpO2 of 97%, urine protein of +4, hemoglobin of 5.2 g%, and fetal heart rate of 144 beats per minute. Vaginal toucher examination showed cervical dilation of 1 cm, negative for amniotic fluid leakage, and cephalic presentation. Laboratory examination results showed leukocytes 17.2, segmented neutrophils 91%, lymphocytes 5%, monocytes 4%, hematocrit 15%, and platelets 71 x 10^3 uL. Complications during the patient's treatment included pneumonia, metabolic acidosis, anemia, melena, and coagulopathy. It is occurred after the patient received treatment in the hospital (two days in the hospital).

Table 1. Frequency distribution of physical examination results in pregnant women with Severe Pre-Eclampsia (PEB) and Anemia

Category	Examination Result	Normal Value	Conclusion
Blood Pressure	156/112 mmHg	<120/80 mmHg	Hypertension
Temperature	38.0°C	36.5°C - 37.5°C	Hyperthermia
Heart Rate	107 beats/min	60-100 beats/min	Tachycardia
Respiration Rate	30 breaths/min	12-20 breaths/min	Tachypnea

From table 1, we can observe the physical examination results in this case show an increase in blood pressure, namely 156/112 mmHg, indicating hypertension; an increase in body temperature to 38.0°C, indicating hyperthermia; an increase in heart rate to 107 beats per minute, indicating tachycardia; and an increase in respiration rate to 30 breaths per minute, indicating tachypnea.

Table 2. Frequency distribution of laboratory examination results in pregnant women with Severe Pre-Eclampsia (PEB) and Anemia

Category	Examination Result	Normal Value	Conclusion
Hb	5.2 gr%	>11 gr%	Anemia
Hematocrit	15 %	40-50 %	Low/Anemia
Monocytes	4 %	2-8 %	Normal
Lymphocytes	5 %	20-40%	Lymphopenia
Segmented Neutrophils	91 %	50-70 %	High
Leukocytes	17.2 x 10^3 uL	5.0-10.0 x 10^3/µl	Leukocytosis
Platelets	71 x 10^3 uL	150-400 x 10^3/µl	Thrombocytopenia
Urine Protein	+4	Negative	Pre-Eclampsia
SGOT	85	5-40 IU/L	High
SGPT	93	7-56 IU/L	High

From table 2, we can observe the laboratory examination results in this case show Anemia is detected with a Hemoglobin level of 5,2 gr%, supported by a low hematocrit level indicating anemia. There is a decrease in lymphocytes (5%) indicating lymphopenia, and an increase in leukocytes (17.2 x 10^3/µl) indicating leukocytosis. There is decrease in platelets (71 x 10^3 uL) indicating thrombocytopenia. One indicator of coagulopathy is platelet count (Thrombocytopenia). Additionally, urine protein is detected at +4, indicating Severe Pre-Eclampsia.

DISCUSSION

SARS-CoV-2 and Pregnancy

Pregnant women are a vulnerable group to experience health disorders, especially infectious diseases, due to changes in their body's physiology and immune response mechanisms [6]. SARS-CoV-2 can infect pregnant women from early pregnancy or the first trimester to the third trimester. In the early stages of pregnancy, SARS-CoV-2 infection has the potential to affect organogenesis and fetal development, increasing the risk of miscarriage. COVID-19 infection can lower immunity in pregnant women and may affect the flow of nutrients and oxygen to the fetus through the placenta [7]. Along with changes in gestational age, the mechanisms of adaptive immune response also change. The first trimester is referred to as the proinflammatory stage to support embryo implantation. The second trimester is referred to as the anti-inflammatory stage; this stage is crucial for maintaining fetal growth, and the third trimester is referred to as the proinflammatory stage as it approaches delivery time [8]. In this case study, it is reported that SARS-CoV-2 infection occurred in a pregnant woman in the third trimester or late trimester at 31 weeks of gestation. The late stage of pregnancy is commonly referred to as the proinflammatory stage as it approaches delivery time, and this mechanism underlies why the majority of COVID-19 cases in pregnancy occur in the late trimester [9].

Screening should ideally be conducted at the first contact with healthcare facilities, including a medical history that includes contact history, physical examination for increased temperature and respiratory rate, laboratory tests, and imaging (WHO, 2020). The clinical manifestations of COVID-19 infection during pregnancy are not different from viral infections in general. Symptoms include fever (53%), cough (42%), shortness of breath (12%), headache, and loss of smell or anosmia [10,11]. The physical examination results in this study also revealed similar symptoms to previous research, including an increased body temperature of 38.0°C, increased heart rate of 107 beats per minute, and increased respiratory rate of 30 breaths per minute.

The diagnosis of COVID-19 in pregnancy is determined similarly to non-pregnant women, based on clinical symptoms and RT-PCR testing as the gold standard diagnosis. Other supportive tests such as laboratory examinations, including complete blood count, white blood cell differential count, C-reactive

protein (CRP), and rapid antibody tests, are also recommended for screening. Increased CRP levels and decreased lymphocyte counts have been found in pregnant women with COVID-19. Calculation of the neutrophil-to-lymphocyte ratio is easy to perform and can be used as one of the screening methods, but its value is greatly influenced by conditions such as preeclampsia, HELLP syndrome, gestational diabetes, ectopic pregnancy, and hyperemesis gravidarum [10]. In this case report the results of laboratory examination were obtained showed a decrease in lymphocyte count (5%) and an increase in leukocyte count (17.2 x 10^3/µl). Other laboratory examination results revealed anemia with a Hemoglobin level of 5.2 gr%, Urine Protein of +4, indicating severe pre-eclampsia and decrease in platelets (71 x 10^3 uL) indicating thrombocytopenia.

From these examination results, it can be observed that pregnant women with Covid-19 can experience complications during pregnancy. This is because overall T-cell activity during pregnancy decreases, and T-cells increase during infection. This relates to the function of T-cells, which can attack virus-infected cells. CD8+ T-cells during pregnancy remain at normal levels. CD8+ cells, which have cytotoxic properties, increase their activity when pregnant women are infected with a virus. This result is associated with the theory that cellular immune responses are more active during viral infections. Studies investigating exhausted T-cells, which are T-cells that have been repeatedly exposed to antigens, have largely diminished function, and senescent T-cells, which are T-cells that have lost their ability to proliferate but can still perform their effector cell functions, also play a role [12]. Shifting Th1/Th2 occurs during pregnancy, with Th1 decreasing while Th2 increases. This is why pregnancy makes both the mother and fetus highly susceptible to infection. Th1 cells function in inflammatory conditions, while Th2 cells function in allergic mechanisms. Th1 activity creates a proinflammatory condition, whereas Th2 activity creates an anti-inflammatory condition [12].

SARS-CoV-2 and Pre-Eclampsia

Preeclampsia is a condition that complicates pregnancy, posing significant risks to the health of both the mother and the fetus, and may result in induced preterm delivery. Preeclampsia occurs in approximately 2–4% of pregnancies, and its exact etiology remains not fully understood. However, it is believed to involve maternal vascular malperfusion and cardiovascular maladaptation due to an imbalance of angiogenic factors, endothelial dysfunction, coagulopathy, and inadequate complement regulation [13]. Pregnant women infected with COVID-19 have a 4.045 times higher risk of developing preeclampsia compared to those who are not infected. Previous studies have indicated a significant relationship between COVID-19 infection and the occurrence of preeclampsia [14].

Pregnant women are particularly vulnerable to COVID-19 infection due to an increase in ACE2 receptors, especially in the placenta. The coronavirus binds to ACE2 to enter human cells, causing dysregulation of the renin-angiotensin-aldosterone system and an imbalance in the ratio between angiotensin-II and angiotensin-1-7, inducing manifestations resembling preeclampsia. The binding of the virus to ACE2 downregulates the conversion of angiotensin II to angiotensin I, leading to increased levels of angiotensin II. This results in endothelial dysfunction, vasculopathy, and thrombus formation, which are also observed in preeclampsia [15]. From the explanation above, it is evident that both the mother and fetus are highly vulnerable to infection. Therefore, a pregnant woman must maintain her health by adopting a clean and healthy lifestyle, as her body's defenses are inadequate to fully perform various physiological functions. The immunity of a pregnant woman can attack the fetus if she is in an inflammatory condition. This could disrupt fetal development, cause permanent abnormalities in the fetus, and even lead to miscarriage due to inflammatory processes [10].

Preeclampsia is characterized by elevated blood pressure and the presence of protein in the urine and is associated with various hematological changes, particularly those affecting the coagulation cascade. Thrombocytopenia, or a low platelet count, is the most common hematological abnormality in preeclampsia and eclampsia [16]. In this case, the pregnant woman's blood pressure was recorded at 156/112 mmHg (hypertension), urine protein was +4 (preeclampsia), and platelets were 71 x 10^3/µL (thrombocytopenia). Hypertension in pregnancy is defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg measured twice, 4 hours apart, while at rest. Hypertension is a diagnostic criterion required for the preeclampsia syndrome. Proteinuria in preeclampsia results from increased permeability of the renal tubules

to large molecular weight proteins such as albumin, globulin, transferrin, and hemoglobin. Proteinuria may take up to 2 years to resolve after preeclampsia, with the severity of preeclampsia and time to delivery positively correlated with recovery time. Thrombocytopenia (platelets <100,000) is likely caused by increased platelet activation, aggregation, and consumption. It has been hypothesized that syncytiotrophoblasts release extracellular vesicles that enhance platelet activation, leading to the release of soluble factors and extracellular vesicles, which may contribute to placental and systemic microvascular ischemia [17].

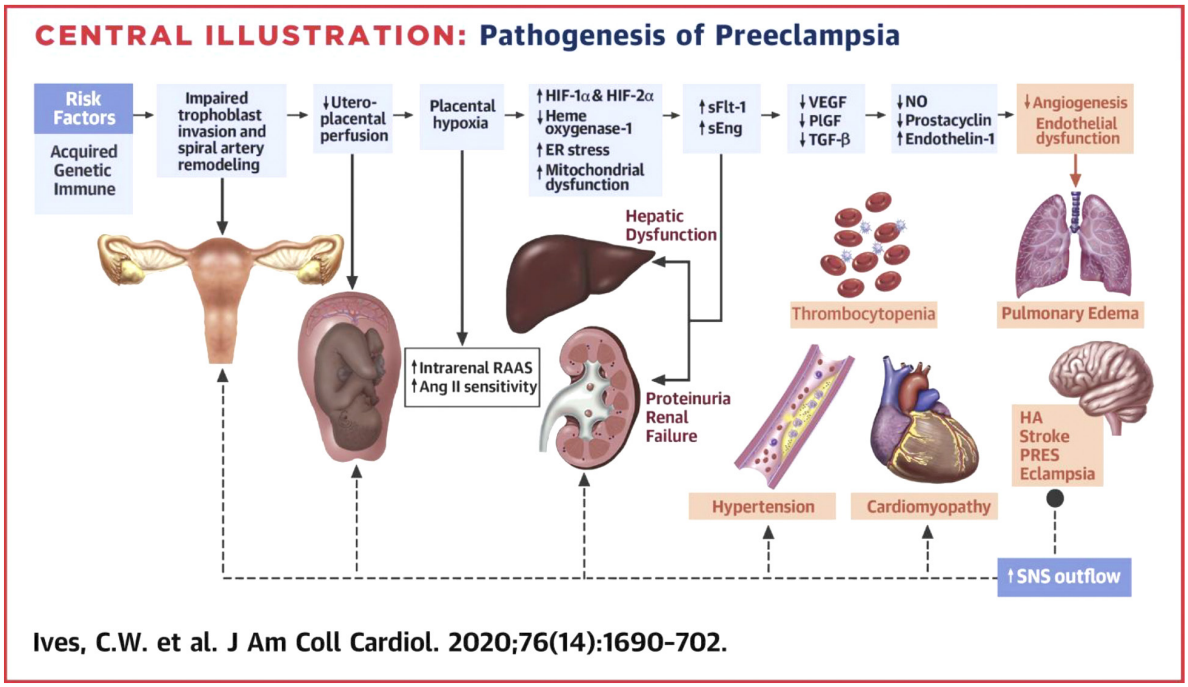

Figure 1. Acquired, genetic, and immune risk factors contribute to early placental dysfunction (Stage 1). Placental dysfunction results in the release of antiangiogenic factors, leading to later multiorgan dysfunction (Stage 2). Solid arrows indicate disease progression. Dashed arrows indicate SNS effects on respective organs. Ang II = angiotensin II; ER = endoplasmic reticulum; HA = headache; HIF = hypoxia-inducible transcription factor; NO = nitric oxide; PlGF = placental growth factor; PRES = posterior reversible encephalopathy syndrome; RAAS = renin-angiotensin-aldosterone system; sEng = soluble endoglin; sFlt = soluble fms-like tyrosine kinase; SNS = sympathetic nervous system; TGF = transforming growth factor; VEGF = vascular endothelial growth factor.

SARS-CoV-2 and Anemia

The immunological and hematological changes during pregnancy increase the risk of COVID-19 infection and anemia in pregnant women [18]. COVID-19 infection in pregnant women can affect hemoglobin (Hb) levels and directly attack the respiratory system, leading to respiratory failure and hypoxia. Hypoxia triggers inflammation and disrupts iron metabolism, making it difficult for the body to absorb iron. This results in decreased iron availability for erythropoiesis, worsening anemia in pregnant women, and potentially causing multi-organ dysfunction syndrome in pregnant patients with COVID-19. This occurs because COVID-19 infection exacerbates anemia [19].

When the COVID-19 virus attacks the immune system, the innate immune response activates hepcidin. Hepcidin is the primary regulator of iron entry into the bloodstream and functions by inhibiting ferroportin. Ferroportin is a transmembrane protein responsible for transporting iron out of cells. Its inhibition traps iron within reticuloendothelial macrophages, ultimately reducing Hb levels in the blood. Furthermore, COVID-19 can attack the respiratory system, causing the lower respiratory tract to release pulmonary infiltrates, which worsens oxygen and carbon dioxide circulation. As the virus enters through the respiratory system, it can cause respiratory failure, leading to hypoxia. This triggers inflammation and changes in iron metabolism, further reducing Hb levels in the blood and leading to anemia [19].

Previous study states that without sufficient iron, the body cannot produce hemoglobin to form red blood cells, which leads to anemia.

Anemia causes an increase in corticotrophin-releasing hormone (CRH) synthesis due to tissue hypoxia, which then results in uteroplacental insufficiency and disrupts blood supply to the fetus. This aligns with the theory of placental ischemia in the pathophysiology of preeclampsia. Ischemic and hypoxic placenta stimulates the formation of oxidants/free radicals, which can damage cell membranes rich in unsaturated fatty acids, leading to lipid peroxidation (20).

CONCLUSION

Abnormal laboratory results in pregnant women with COVID-19 can indicate the severity of the condition. These laboratory findings can help determine prognosis early on, allowing for early intervention in the hope of improving the patient's condition. COVID-19 virus infection in pregnant women can increase the risk of complications during pregnancy. This is because pregnant women are considered a vulnerable group experiencing physiological changes in their bodies and alterations in their immune response.

CONFLICT OF INTEREST

This research is a personal study funded internally by Universitas dr. Soebandi, and there are no conflicts of interest in this research.

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