

## **Treatment of Pulmonary Edema in Severe Preeclampsia during Pandemic**

### **Abstract**

Pulmonary edema is a rare complication of preeclampsia, but has a high morbidity rate and can be life threatening. Shortness of breath is the main symptom for patient with both pulmonary edema and moderate to severe COVID-19 infection. The COVID-19 pandemic is a big challenge for all clinicians in various parts of the world. Both COVID-19 infection and severe preeclampsia could share the same symptoms such as shortness of breath. Prompt and precise diagnosis must be made without forgetting the possibility of COVID-19 infection or pulmonary edema that occurs as a complication of COVID-19 infection. This paper was written by conducting a literature review and analysis of several literature articles and case reports. This paper is expected to provide information about the management of pulmonary edema caused by preeclampsia during this pandemic.

Key words : pulmonary edema, COVID-19, preeclampsia

### **Introduction**

Pulmonary edema is a medical emergency that requires quick and precise treatment. Pulmonary edema is one of the rare but deadly complications of preeclampsia. It can cause death in patients with preeclampsia and is the most common cause of ICU admission in pregnant mothers. Pulmonary edema is fluid accumulation in lung interstitial space and alveolus that disturbs oxygen and carbon dioxide diffusion. It is characterized by shortness of breath which is sometimes accompanied by restlessness.<sup>1</sup>

Pulmonary edema occurs in 3% of patient with preeclampsia during pregnancy and 70% after birth. Several identified risk factors for this disease are tocolytic therapy usage, severe infection, heart disorder, fluid overload, and multiple pregnancies.<sup>2</sup>

The ongoing pandemic has become a challenge in the medical field, either in diagnosis or treatment. Varieties of clinical manifestation make recognition of disease harder. COVID-19 with mild symptoms become the source of transmission. On the other hand, severe COVID-19 become a challenge in diagnosis and treatment considering the ongoing studies about the disease.

Symptoms such as fever, cough, cold and swallowing pain have similarities with other respiratory infections caused by other pathogens. Shortness of breath also opens up tons of differential diagnosis, from heart disorders such as heart failure and **pericardial** effusion to lung disorders like bacterial pneumonia and pulmonary edema.<sup>1,2</sup>

Considering the similarities of symptoms between COVID-19 and pulmonary edema, special precautions should be taken. Transmission risk during treatment should be considered because airway management involves aerosol-generating procedures (AGP).<sup>1,2</sup>

### **Cardiovascular Disorder and Pulmonary Edema**

Pulmonary edema in pregnant and non-pregnant mothers is affected by a tension that causes the fluid transfer to the lungs. The difference between those two groups of patients is body physiology condition in which there is specific pathophysiology occurring in patient with preeclampsia. Another aspect is the crucial and critical treatment approach to ensure fetus safety.<sup>2,3</sup>

Acute pulmonary edema can be caused by various disorders of factors that play a crucial role in cardiovascular function and fluid flow to the pulmonary interstitial. Hydrostatic pressure, colloid osmosis pressure and capillary permeability are three factors determining the amount of fluid in lung interstitial, which is summarized in Starling Law:

Transcapillary fluid filtration rate  $\propto K_f [ (P_{mv}-P_t) - (COP_{mv} - COP_t)]$

\*K<sub>f</sub> is ultrafiltration coefficient, capillary permeability, P<sub>mv</sub> is microvascular pressure, P<sub>t</sub> is tissue hydrostatic pressure; COP<sub>mv</sub> is microvascular colloid osmotic pressure.<sup>2</sup>

Hydrostatic pressure depends on heart function, including preload, heart rate, contractility, myocardium relaxation ability (lusitropy) and afterload. Hydrostatic pressure is also determined by artery and vein vascular tone. The respiratory system regulates the tone itself and vasoactive substances in the circulation

system. Systemic and pulmonary circulations perform their function parallel with cardiac output and venous return. The Frank-Starling mechanism can be applied in stroke volume from both ventricles. This mechanism means that either acute pulmonary oedema or complete clearance of pulmonary circulation can occur, and both events lead to fatal consequences. Equilibrium in this system is characterized by cardiac output achieved at the lowest ventricular end-diastolic pressure that can still fulfil tissue metabolic demands and venous return. Acute pulmonary edema represents an imbalance system that can no longer meet tissue metabolic demands. Therefore, factors increasing hydrostatic pressure that cause high left ventricular end-diastolic pressure, factors decreasing colloid osmotic pressure or factors increasing capillary permeability will affect acute pulmonary edema incidence.<sup>2</sup>

### **Pulmonary Edema Pathogenesis in Preeclampsia**

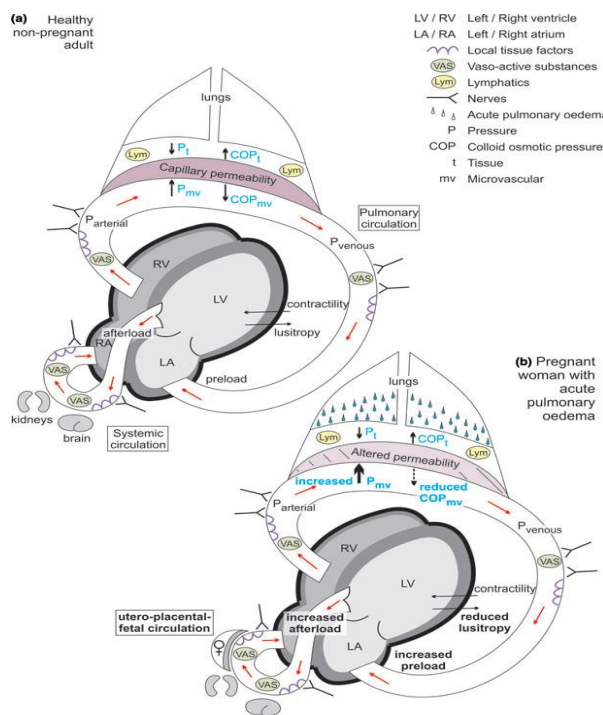
Preeclampsia is a specific pregnancy condition characterized by placenta dysfunction and maternal response towards systemic inflammation through endothelium activation and coagulation. Preeclampsia diagnosis is made based on particular hypertension caused by pregnancy accompanied by other organ dysfunctions at gestational age above 20 weeks. Preeclampsia can also be defined as a multisystemic cardiovascular disorder marked by hypertension and clinical manifestation associated with hypertension complication itself.<sup>3</sup>

Women with preeclampsia have varying degrees of cardiac abnormalities, from abnormal cardiac output increase, the moderate elevation of vascular resistance or low cardiac output with increased systemic vascular resistance. Ventricle diastolic function can also be impaired. It is seen from an increased left ventricular mass that is sometimes accompanied by pericardium effusion.<sup>2,4</sup>

Preeclampsia can also decrease plasma colloid osmotic pressure, impair capillary permeability, and decrease osmotic pressure to end-diastolic volume. The underlying mechanism of acute pulmonary edema in this condition depends on the hemodynamic state in pregnant women. Besides structural and functional heart diseases, changes in a fluid balance associated with hypo-proteinuria can also be

observed. A reduced ventricle ejection fraction shows the presence of significant residual blood in the heart that is not pumped. In this condition, the heart cannot produce enough cardiac output to deliver oxygen to other vital organs.<sup>2,4</sup>

Acute hypertensive crisis triggers acute pulmonary edema by activating the sympathetic nervous system, which causes an increase in afterload and fluid redistribution from the peripheral circulation to pulmonary vascularization. This event leads to fluid accumulation in the alveolus, decreased oxygenation and indirect growth of cardiac output as a compensation mechanism due to a decrease of oxygen distribution to the kidneys<sup>2</sup>



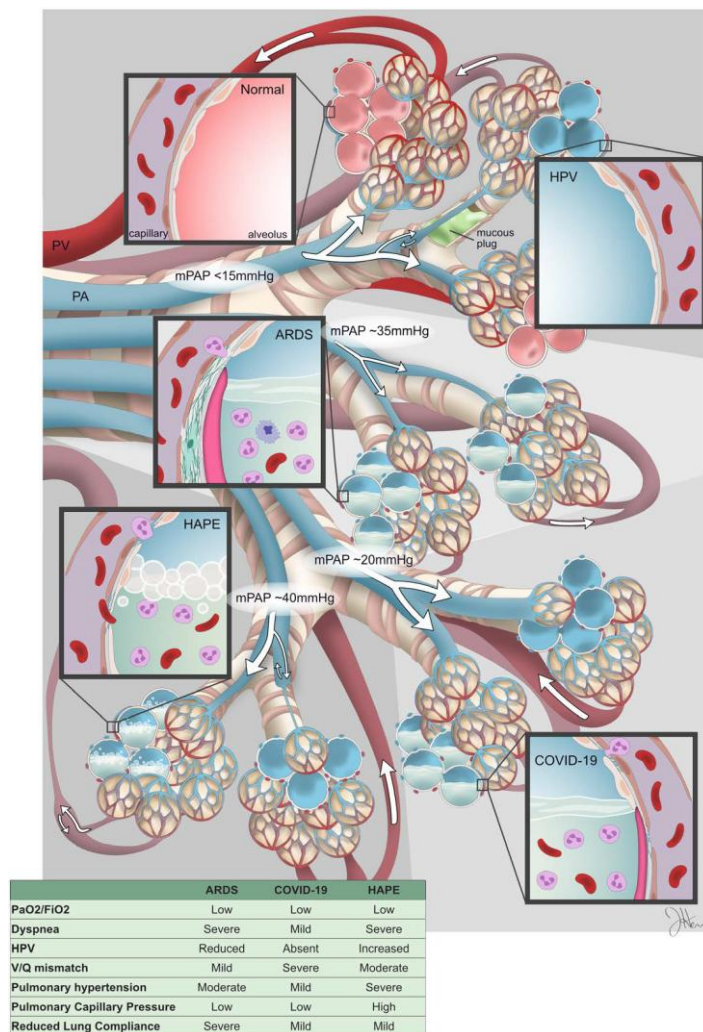
**Figure 1. Filtration pressure in non-pregnant healthy adults (a) and women with preeclampsia and acute pulmonary edema (b). An increase of afterload is caused by hypertension and a decrease in lusitropy due to left ventricle structural changes in left ventricle hypertrophy. This leads to elevation of microvascular pressure and preload. The lowering of colloid osmotic pressure combined with changes in capillary permeability increases the risk of acute pulmonary edema.<sup>2</sup>**

## **Pulmonary Edema in COVID-19**

COVID-19 is currently aggravating the condition of patients with pulmonary edema, both in pregnant women with or without preeclampsia. Few expectant mothers with severe COVID-19 symptoms had similar manifestations with severe preeclampsia known as HELLP syndrome. Patients with COVID-19 pneumonia can experience decompensation due to hypoxemia breathing failure. Data from an autopsy showed inflammation, diffuse alveolar injury, alveolar fluid accumulation that was sometimes accompanied by hyaline membrane disease was consistent with acute respiratory distress syndrome (ARDS). The process of understanding hypoxemia etiology in COVID-19 becomes more complicated with a lack of data regarding hemodynamic and autopsy results. ARDS in COVID-19 can also be atypical because heavy hypoxemia can happen without a severe complaint of shortness of breath.<sup>5</sup>

Hypoxic pulmonary vasoconstriction (HPV) is a pulmonary circulation response to maintain homeostasis when airway hypoxia happens in respiratory diseases like pneumonia. HPV will constrict the pulmonary artery in the hypoxic lung segment and divert blood flow to alveoli that still has good ventilation to optimize ventilation and perfusion suitability. Carotid body will then detect hypoxemia and increase respiratory rate.<sup>5,6</sup>

Recently, high altitude pulmonary edema (HAPE) physiology has been suggested as the mechanism for edema and hypoxemia in COVID-19 pneumonia. HAPE is caused by veno-constriction and HPV in certain lung region. Pulmonary edema in HAPE happens due to HPV and is characterized by a high mean value of pulmonary artery pressure, 45-60 mmHg. The essential aspect of these changes is HPV without lung involvement. Hence, lung vascular that doesn't experience vasoconstriction will undergo an increase in pressure and blood flow. The pressure will increase pulmonary artery and capillary pressure, leading to capillary hydrostatic damage and blood and protein leakage. HPV in COVID-19 is possibly reduced. Alveolar infiltrates produced from the inflammation process, and pulmonary artery pressure becomes low.<sup>5,6</sup>



**Figure 2. Difference of lung hemodynamic in ARDS, COVID-19 pneumonia and HAPE.** <sup>5</sup>

The figure above should be read from upper left to lower right clockwise. The summary of each syndrome is made into a green list. HPV diverts blood away from the hypoxia alveolar segment caused by mucus blockage on the upper left bronchus. Blood from this segment is directed towards the alveolus with good vascularization. There are no injuries in the alveolus, and segmental HPV does not increase average pulmonary artery pressure or cause dyspnea. In ARDS, the primary dysfunction happens because of alveolar injury due to inflammation associated with pulmonary hypertension. HPV promotes V/Q mismatch and worsening hypoxemia. If the damage continues, the lung becomes stiff and

fibrotic (green fibrous tissue and fibroblasts in alveolus walls) with the hyaline membrane in the alveolus (pink scythe).<sup>6,7</sup>

In ARDS, pulmonary hypertension often occurs due to thrombosis and endogenous vasoconstriction instead of HPV. Although HAPE and ARDS are both types of noncardiogenic pulmonary edema, they are triggered by different events. HAPE is a primary hemodynamic problem in the pulmonary artery and vein. Edema in ARDS is the result of inflammation and alveolar epithelial dysfunction. In severe COVID-19 pneumonia, ARDS findings can be seen, but the consequences are far worse due to the loss of HPV. The distinction between HAPE and impaired HPV in COVID-19 has beneficial therapeutic implications. The HAPE hypothesis, combined with the assertion that HPV inhibition using acetazolamide, calcium channel blockers or phosphodiesterase-5-inhibitor, will worsen hypoxemia in COVID-19 pneumonia. Many patients with COVID-19 have systemic hypertension (15%), and to avoid systemic vasodilators, particularly calcium channel blockers, will preserve HPV.<sup>6,7</sup>

Several disorders are similar to preeclampsia (PE). Pathophysiological causes of such phenomena include vasospasm, platelet activation or destruction, microvascular thrombosis, endothelial dysfunction, and reduced tissue perfusion. The referred disorders are gestational hypertension, chronic kidney disease, fatty liver in pregnancy, thrombocytopenic thrombotic purpura, hemolytic uremic syndrome, acute exacerbation of systemic lupus erythematosus, severe hypothyroidism, and sepsis. Moreover, some of those are potentially life-threatening to both mother and fetus. Therefore, an accurate diagnosis is essential to decide the management and prognosis of those conditions, which are very different. Recent studies have shown that an examination of angiogenic factors is necessary to rule out the differential diagnosis between PE and some of its imitators, particularly COVID-19.<sup>5,6,7,8</sup>

### **Risk Factors and Prevention of Pulmonary Edema in Preeclampsia**

Predisposition factors of pulmonary edema in preeclampsia patients include the history of chronic hypertension, overload colloid and crystalloid fluid administration, massive proteinuria, decreased albumin serum, oliguria, increased creatinine serum because of kidney injury, and multiple pregnancies.<sup>9</sup>

Based on published literature, anemia is positively linked to pulmonary edema. Body condition with hyperdynamic circulation due to anemia increases the risk of pulmonary edema. This phenomenon might be caused by the decreased basal endothelial inhibition process caused by vasodilation due to reduced Hb concentration, blood pressure, neurohormonal activation.<sup>9</sup>

Preeclampsia risk also increases in multiple pregnancies that cause dysfunction in angiogenic factors, leading to changes in endothelial permeability, so vascular leakage and pulmonary edema can happen.<sup>9,10</sup>

### **Diagnosis of Pulmonary Edema during COVID**

The most common symptom of pregnant mommies with pulmonary edema is shortness of breath. Other than that, orthopnea, agitation, and cough can also be found. The typical clinical signs found in patients include tachycardia, tachypnea, crackles and/or wheezing on chest auscultation, S3 gallop rhythm, heart murmur, and oxygen desaturation.<sup>2,9,10</sup> Oxygen desaturation is usually seen in COVID-19 patients. Hence, COVID-19 should be considered as a differential diagnosis until proven not. Therefore, PCR swabs screening becomes crucial in medical service, especially in patients experiencing shortness of breath.

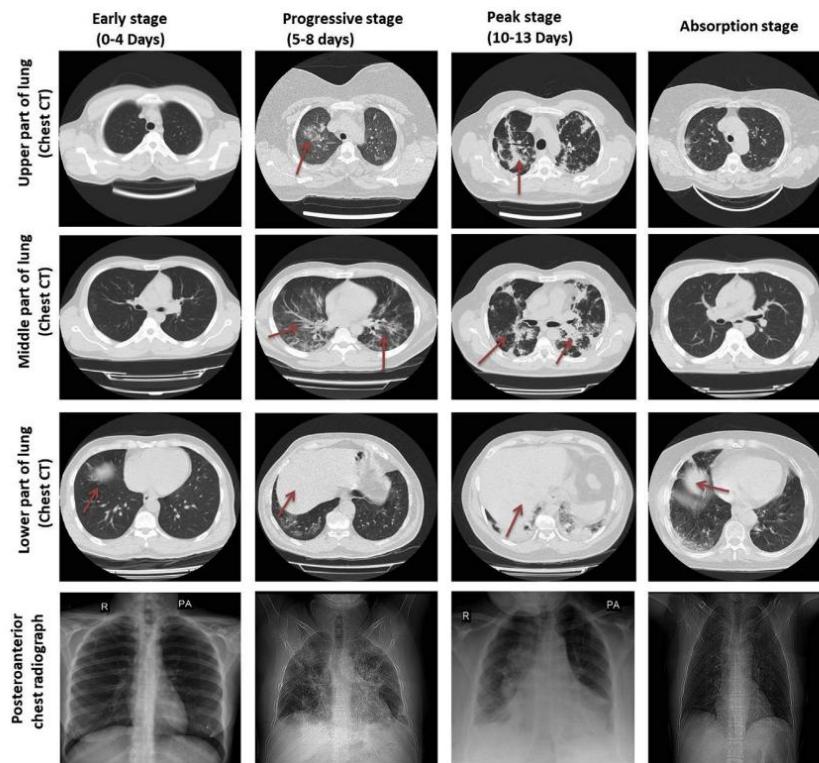
It is vital to include COVID-19 and its sequelae symptoms as a differential diagnosis in a new or exacerbation case with shortness of breath. The same principle applies in the negative COVID-19 RT-PCR nasopharynx test, considering its sensitivity rate of only 70%. Diagnosis uncertainty rises even further when patients have underlying conditions like interstitial lung disease (ILD) and congestive heart failure (CHF) that are clinically and radiologically similar to COVID-19 pneumonitis. Rajendran et al. in 2021 reported that several patients with negative PCR tests had COVID-19 pneumonia-like chest Xray. The



gained result was suspected to happen due to the very low virus load, making it hard for the machine to examine.<sup>11</sup>

When Xray first showed a positive result, COVID-19 manifested in a consistent finding: blurred opacification suspected of correlating with ground-glass opacity (GGO) radiography in CT-Scan. The morphology of GGO is round and distributed in the peripheral and lower segment of the lungs. Chest X-ray findings might be unilateral or bilateral and, along with its progression, can be found more in mid-upper segments. Opacity becomes more apparent and harsher when the disease worsens, known as uneven consolidation. The finding is best observed 10 - 12 days after symptoms appear. Moreover, lung opacity can become diffuse, similar to diffuse alveolar damage seen in acute respiratory distress syndrome (ARDS).

Typical pulmonary edema chest X-ray features are upper lobe redistribution, Kerley-B line, and infiltrates. Things like lung opacity, thickening of bronchial walls, increased markings on lungs interstitial tissue, and blurry vascular appearance might be seen in imaging tests. Arterial blood gas examination will show a decrease in PaO<sub>2</sub>. ECG and echocardiography can help confirm the diagnosis.<sup>11</sup>



**Figure 3. Chest X-Ray and CT-Scan Results in COVID-19 patient. There are 4 stages; 1)early stage (0-4 days) 2)progressive stage (5-8 days), 3)peak stage (10-13 days), and 4)abortion stage**

The difference between normal chest X-Ray and positive RT-PCR test in COVID-19 patients is the lack of pulmonary involvement when the symptoms first appeared, early acquisition of disease, and the subtlety of chest radiology findings, especially in limited anteroposterior portable radiography.<sup>11,12</sup>

Transthoracic echocardiography is the key to diagnosis and treatment. This imaging test allows for measuring cardiac output rate while Doppler tissue assesses heart systolic function. The diastolic function can be measured through Doppler velocity of inflow to the mitral valve (wave E and wave A) and movement of myocardial tissue septum ( $e\phi$  and  $a\phi$ ) that changes ventricular volume and pressure. The velocity ratio in the initial peak inflow of the mitral valve divided by the annular mitral Doppler tissue velocity at the start of diastole is closely related to the left ventricular end-diastolic pressure. A ratio of 15 in nonpregnant adults with reduced ejection fraction, or a ratio of 13 in adults with

an average ejection fraction, indicates an increase in left ventricular end-diastolic pressure. A ratio of  $<8$  indicates low left ventricular end-diastolic pressure and normal diastolic function.<sup>11,12,13</sup>

### **Treatment of Pulmonary Edema in Preeclampsia during COVID**

The goal of pulmonary edema treatment during pregnancy is to lower preload and afterload on the left ventricle, decrease and prevent myocardium ischemia, maintain adequate ventilation and oxygenation also protect itself from infection risk. ABCDE principle remains essential in the treatment algorithm. Airway management treatment should be performed considering the high risk of cardiac arrest in patients. Non-invasive ventilation should be attempted before trachea intubation to increase inspiration volume, make the fluid transfer from alveolus to lung possible, reduce breathing effort to prevent exhaustion, and lower the risk of trachea intubation. Non-invasive ventilation also helps prevent trachea intubation complications during pregnancy, especially in pregnant mothers with preeclampsia like intracerebral hemorrhage.<sup>14</sup>

There was no proof found in a systematic review that evaluated strategy for optimal fluid administration in women with preeclampsia regarding the usage of specific fluid types in preventing pulmonary edema in preeclampsia management protocol. Prophylaxis diuretic can preserve central vein pressure by reducing overload intravascular fluid due to massive autotransfusion and inhibit diuresis in preeclampsia women. Intravenous furosemide administration with the dosage of 20-40 mg in 2 minutes is used for the veno-dilation mechanism. The drug can be repeated with a 40-60 mg dose if no adequate response is observed in 30 minutes. The maximum dose is 120 mg. Two randomized control studies had assessed the furosemide effect when taken orally in a dose of 20 mg among preeclampsia women after 3 to 5 postpartum days. Results showed furosemide could help normalize blood pressure faster and lower the need for anti-hypertension therapy.

<sup>15,16</sup>

Optimal hypertension treatment is prescribed based on the underlying hemodynamic condition. Options for therapy among women with vasoconstriction are vasodilators such as calcium channel blockers like nicardipine and nifedipine. In vasoconstrictive hypertensive patients, oral labetalol should be avoided due to adverse inotropic effects leading to lower cardiac output. An immediate blood pressure drop should be done in emergency hypertension using intravenous antihypertension drugs. Nitroglycerine (glyceryl trinitrate) is recommended for pregnant preeclampsia patients. Other available alternatives are sodium nitroprusside and intravenous furosemide. The target of systolic and diastolic blood pressure drop should be around 30 mmHg in 3 - 5 minutes or 140/90 mmHg.<sup>15,16</sup>

## **Conclusion**

Pulmonary edema is a complication of severe preeclampsia that causes high morbidity and mortality in pregnant mothers. One common symptom found among patients is shortness of breath. Therefore, clinicians should be cautious in ruling out the possibility of COVID-19 by doing screening through PCR swab and imaging examinations such as chest X-Ray or CT-Scan, considering immunoserology interpretation test relies on viral load. Pulmonary edema treatment follows the ABCDE principle and upholds the value of minimizing infection risk. Non-invasive ventilation has become the primary choice as aerosol size is tiny and has been proven to prevent intracranial bleeding. Diuretic plays a crucial part in decreasing preload to inhibit interstitial fluid accumulation and ensure ventilation and diffusion keeps going well. Blood pressure should be monitored so cardiac output and adequate oxygen perfusion can be maintained.

## **Ethical Approval:**

As per international standard or university standard ethical approval has been collected and preserved by the authors.

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