

Factors Associated with Pulmonary Edema among Severe Pre-Eclamptic Women: A Case Control Study

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Background: Pre-eclampsia remains an important cause of hypertensive acute pulmonary edema in pregnancy. Acute pulmonary edema, which signifies severe disease, is a leading cause of death in pregnant women with pre-eclampsia and a frequent cause of admission to intensive care unit.

Objective: To examine pulmonary edema's prevalence and associated factors among severe pre-eclamptic pregnant women.

Materials and Methods: The present study was an analytic retrospective case-control study. Five hundred fifty-eight gestational-age pregnant women diagnosed with pre-eclampsia with severe features according to the ACOG 2013 guidelines delivered at Pattani Provincial Hospital between July 2021 and April 2023 were enrolled by retrospective review the hospital records. Four hundred severe pre-eclamptic women met the inclusion criteria. Fifty-one pregnant women with severe pre-eclampsia who developed pulmonary edema were included as cases, and 204 severe pre-eclamptic women who did not develop pulmonary edema were included in cases for a ratio of 1 to 4. The statistical analyses involved the two groups. Multiple logistic regression analysis, odd ratio, and 95% confidence interval (CI) were performed.

Results: Among severe pre-eclamptic pregnant women, the associated factors for severe preeclamptic women decreased 69% (95% CI 0.1 to 0.9) with nulliparous, decreased 88% (95% CI 0.0 to 1.1) with the first blood pressure level of more than 180/120 mmHg, decreased 98% (95% CI 0.0 to 0.1) with epigastric pain as presenting symptoms. However, the associated factors for pulmonary edema increased 2.04 (95% CI 1.0 to 4.0) times with the number of antenatal care visits of less than eight times and increased 2.79 (95% CI 1.4 to 5.6) times with gestational diabetes mellitus.

Conclusion: The prevalence of pulmonary edema among severe pre-eclamptic women was 12.75%. The factors associated with pulmonary edema among severe pre-eclamptic women included gestational diabetes mellitus and poor antenatal care of less than eight visits.

Keywords: Severe pre-eclampsia; Pulmonary edema

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Pre-eclampsia remains an important cause of hypertensive acute pulmonary edema in pregnancy. The preventive strategies include close clinical monitoring and restricted fluid administration⁽¹⁾. Pre-eclampsia is a multisystem major cardiovascular disease of pregnancy with hypertension as its main clinical manifestation⁽¹⁻³⁾. Acute pulmonary edema, which signifies severe disease, is a leading cause of death in women with pre-eclampsia and a frequent cause of admission to intensive care unit^(1,4).

Pre-eclampsia also leads to a reduction in

plasma colloid osmotic pressure, altered endothelial permeability, and reduced colloid osmotic pressure to the left ventricular end-diastolic pressure gradient^(1,5). The underlying mechanism of acute pulmonary edema in these circumstances depends on the underlying hemodynamic state of the pregnant woman. Not only cardiac structural and functional abnormalities, but there are also alterations in fluid balance associated with hypoproteinemia^(1,6).

Pulmonary edema is the most common cardiopulmonary complication of pre-eclampsia, occurring in 3% to 5% of preeclamptic pregnancies, mainly in the peripartum or postpartum stage. Seventy percent of pulmonary edema events occur in the postpartum period. Following the placental removal, a fluid shift from the extravascular space restores the intravascular volume, increasing the preload. Furthermore, the inadvertent administration of fluid, frequently used to increase plasma volume or treat oliguria, may also exacerbate that iatrogenic fluid administration, a major preventable action in pulmonary edema⁽⁶⁾.

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Studies have been done to determine the risk factors of pulmonary edema in severe pre-eclamptic women. These studies lead us to continue to discover more interesting associated factors. As a result, future studies may be directed at examining these factors to prevent and treat pulmonary edema in severe pre-eclamptic women with successful technique.

From literature reviews, associated risk factors for pulmonary edema in severe pre-eclamptic women were as follows.

In a 2018 study, Keepanasseri et al. reported pulmonary edema developed in 2.67% of the pre-eclamptic women. Nulliparous preeclamptic women were found to be an increased risk of developing pulmonary edema.

In a 2018 study, Wardhana et al., reported that the prevalence of pulmonary edema in severe pre-eclamptic women was 5.6%. Pulmonary edema was a common complication of preeclampsia in Indonesian referral hospitals. This severe complication increased maternal and perinatal morbidity and mortality. Postpartum and cesarean delivery proportions were higher in the pre-eclampsia with pulmonary edema. Of these pulmonary edema cases, 81% required intensive care admission.

In a 2020 study, Keepanasseri et al., reported that pulmonary edema was a potentially life-threatening complication of pre-eclampsia. The association between various potential risk factors and the development of pulmonary edema were nulliparity, multifetal pregnancy, mean arterial blood pressure in mmHg and mild or moderate anemia. At the same time, early aggressive blood pressure treatment can reduce the risk of pulmonary edema.

In a 2023 study, Bushra et al., reported the prevalence of pulmonary edema in severe pre-eclamptic women was 2.1%. Pulmonary edema is associated with adverse maternal outcomes among patients with severe pre-eclampsia and is more likely to affect nulliparous patients, who have an autoimmune disease diagnosed preterm.

For all the above reasons, the authors were interested in studying the prevalence and associated factors of pulmonary edema in severe pre-eclamptic Thai pregnant women. The result of the present study could help physicians counsel severely pre-eclamptic women about the associated factors for the development of pulmonary edema, including developing a maternal and child health service system to monitor these associated factors to cover all forms of proactive care. However, there has been no such study in Thailand, especially in Pattani Province,

which is often found to be an area where severe pre-eclampsia is more common than anywhere else. Thus, the authors believed that the genetics, race, body structure, lifestyle, characteristics, and environment of Pattani, Thailand differ from other countries. The authors, the obstetricians, and the team have been facing every day, pregnant women with pre-eclampsia and the number has been on an upward trend to date. The present study played an important role in making the facts apparent. A new ACOG 2013 diagnostics definition for the severe feature of pre-eclampsia was used to select the study population. The present study aimed to determine associated factors of pulmonary edema among severe preeclamptic women; in a case-control study from Pattani Hospital, Thailand. The result of the study would be used to stimulate the maternal and child health service system and to work more proactively at the source of the problem as well as possible preventive measures.

Materials and Methods

An analytic retrospective case-control study was conducted at the Department of Obstetrics and Gynecology, Tertiary Care Referral Center in Pattani Provincial Hospital, Thailand. Five hundred fifty-eight certain gestational age pregnant women diagnosed with pre-eclampsia with severe features according to the ACOG 2013 guidelines, delivered at Pattani Provincial Hospital between July 2021 and April 2023 were enrolled by retrospective review of the hospital records. Four hundred severe preeclamptic women met the inclusion criteria. Fifty-one pregnant women with severe pre-eclampsia who developed pulmonary edema were included as cases, and 204 severe preeclamptic women who did not develop pulmonary edema were the controls, for a ratio of 1 to 4.

Severe features of pre-eclampsia were defined as a new onset of hypertension after 20 weeks gestation with any of these findings according to the ACOG guidelines⁽⁷⁾, which were 1) systolic blood pressure of 160 mmHg or higher, or diastolic blood pressure of 110 mmHg or higher on two occasions at least four hours apart while the patient is on bed rest, unless antihypertensive therapy was initiated before this time, 2) thrombocytopenia with platelet count of less than 100,000 per microliter, 3) impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes with two twice normal concentrations or severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative

Table 1. Maternal characteristics of pulmonary edema (PE) in severe pre-eclamptic women; univariate analysis, student t-test

Maternal characteristics	Severe pre-eclampsia; mean±SD		p-value
	With PE (n=51)	Without PE (n=204)	
Maternal age	35.16±6.83	32.89±6.83	0.035*
Number of pregnancies	4.47±2.46	3.17±2.01	<0.001*
Number of antenatal care visits	8.43±3.15	10.15±4.18	0.006*
Systolic blood pressure	180.90±23.12	172.64±14.98	0.002*
Diastolic blood pressure	114.57±16.88	105.01±10.28	<0.001*
Birth weight	2,299.75±832.41	2,682.76±775.60	0.002*
BMI	32.31±4.86	30.98±5.24	0.102
APGAR at 1 minute	8.27±1.48	8.36±2.07	0.775
APGAR at 5 minutes	8.94±1.17	8.91±2.23	0.928

PE=pulmonary edema; BMI=body mass index; SD=standard deviation

* Statistically significant

diagnoses, 4) progressive renal insufficiency as seen with serum creatinine concentration greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease, 5) pulmonary edema, and 6) new-onset cerebral or visual disturbances⁽⁸⁻¹⁰⁾.

Diagnosis of pulmonary edema include commonly associated clinical symptoms such as breathlessness, orthopnea, agitation, or cough, and signs such as tachycardia, tachypnea, crackles, and wheeze on chest auscultation, cardiac S3 gallop rhythm and murmurs, and decreased oxygen saturation. Typical chest X-ray features include upper lobe redistribution, Kerly-B lines, and pulmonary infiltrates. Arterial blood gases with a decreased P_aO_2 , electrocardiogram (ECG), and echocardiography may help establish the diagnosis^(1,6,11).

Four data collectors and lead researchers conducted the data collection. Patient medical records were used to collect the data. The present study divided the participants into two groups as cases and controls. Pregnant women with medical problems that cause hypertension such as autoimmune disease, renal disease, thyroid disease, or cardiovascular diseases, and those with obstetrics conditions such as multiple pregnancies and with fetal conditions such as hydrops fetalis were excluded from the present study.

After obtaining all the data, it was then taken into a statistical analysis program. Characteristics of pregnant women were performed and using the IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set up at a p-value of less than 0.05. Statistical analyses involving two groups, with pulmonary edema and without pulmonary edema, were compared to characteristics of women using chi-square if

variables were categorical, and unpaired student t-test if variables were continuous. If the factors or information was associated with the development of pulmonary edema, a binary and multiple logistic regression analysis, odd ratio, and 95% confidence interval (CI) were performed. The present study was granted ethical approval by Pattani Provincial Hospital Research Ethics Committee No. PTN-037-2566.

Results

The prevalence of severe pre-eclampsia was 6.93% (558 out of 8,400). Pulmonary edema developed in 12.75% (51 out of 400) of the severe preeclamptic women in this period. Pulmonary edema was a common complication of severe pre-eclampsia in Pattani provincial tertiary care hospital.

Table 1 presents the maternal characteristics of pulmonary edema in severe preeclamptic women using univariate analysis. Among severe preeclamptic women who developed pulmonary edema, they were significantly older with a mean maternal age of 35.16±6.83 years. They had a significantly higher mean number of pregnancies of 4.47±2.46 times, a significantly lower mean number of antenatal care visits at 8.43±3.15 times, a significantly higher mean systolic blood pressure at 180.90±23.12 mmHg, a significantly higher mean diastolic blood pressure at 114.57±16.88 mmHg, and a significantly lower mean birth weight at 2,299.75±832.41 grams than severe preeclamptic women without pulmonary edema who had a mean maternal age of 32.89±6.83 years, a mean number of pregnancy of 3.17±2.01 times, a mean number of antenatal care visits of 10.15±4.81 times, mean systolic blood pressure of 172.64±14.98 mmHg, a mean diastolic blood pressure

Table 2. Maternal characteristics of pulmonary edema (PE) in severe pre-eclamptic women; bivariate data analysis, logistic regression

Maternal characteristics	Severe pre-eclampsia; n (%)		OR (95% CI)	p-value+
	With PE (n=51)	Without PE (n=204)		
Age			0.57 (0.3 to 1.1)	0.079
≥35 years	29 (56.9)	88 (43.1)		
<35 years	22 (43.1)	116 (56.9)		
Previous SPIH			3.75 (1.2 to 11.7)	0.016*
Yes	6 (11.8)	7 (3.4)		
No	45 (88.2)	197 (96.6)		
Family history of SPIH			NA	0.090
Yes	0 (0.0)	11 (5.4)		
No	51 (100)	193 (94.6)		
Underlying DM			1.95 (0.7 to 5.4)	0.190
Yes	6 (11.8)	13 (6.4)		
No	45 (88.2)	191 (93.6)		
Underlying HT			1.04 (0.5 to 2.0)	0.894
Yes	17 (33.3)	66 (32.4)		
No	34 (66.7)	138 (67.6)		
Number of pregnancies			0.38 (0.1 to 0.9)	0.031*
G1	6 (11.8)	53 (26.0)		
≥G2	45 (88.2)	151 (74.0)		
1 st gestational age of HT			2.85 (1.5 to 5.4)	0.001*
<37 weeks	34 (66.7)	84 (41.2)		
≥37 weeks	17 (33.3)	120 (58.8)		
BMI at delivery period			0.32 (0.2 to 0.6)	0.042*
≥25 kg/m ²	50 (98.0)	51 (25.0)		
<25 kg/m ²	1 (2.0)	153 (75.0)		
1 st high BP level			0.32 (0.2 to 0.6)	<0.001*
>180/120 mmHg	26 (51.0)	51 (25.0)		
160/110 to 180/120 mmHg	25 (49.0)	153 (75.0)		
Number of ANC visits			2.04 (1.0 to 4.0)	0.033*
<8	18 (35.3)	43 (21.1)		
≥8	33 (64.7)	161 (78.9)		
Gestational DM			2.79 (1.4 to 5.6)	0.003*
Yes	17 (33.3)	31 (15.2)		
No	34 (66.7)	173 (84.8)		
Route of delivery			0.47 (0.2 to 1.0)	0.040*
NL	11 (21.6)	75 (36.8)		
CS	40 (78.4)	129 (63.2)		
Blur vision			2.16 (1.0 to 4.8)	0.053
Yes	11 (21.6)	23 (11.3)		
No	40 (78.4)	181 (88.7)		
Epigastric pain			0.44 (0.2 to 1.0)	0.047*
Yes	8 (15.7)	60 (29.4)		
No	43 (84.3)	144 (70.6)		
Headache			2.19 (1.0 to 4.5)	0.031*
Yes	14 (27.5)	30 (14.7)		
No	37 (72.5)	174 (85.3)		

PE=pulmonary edema; SPIH=severe pregnancy induce hypertension; DM=diabetes mellitus; HT=hypertension; BMI=body mass index; BP=blood pressure; ANC=antenatal care; NL=normal delivery; CS=cesarean section; OR=odds ratio; CI=confidence interval
+ Chi-square, * Statistically significant

Table 3. Maternal characteristics of pulmonary edema (PE) in severe pre-eclamptic women; multiple logistic regression data analysis

Maternal characteristics	Severe pre-eclampsia		Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
	With PE (n=51)	Without PE (n=204)			
Previous SPIH					
Yes	6 (11.8)	7 (3.4)			
No	45 (88.2)	197 (96.6)	3.75 (1.2 to 11.7)	1.54 (0.4 to 6.5)	0.555
Number of gestations					
G1	6 (11.8)	53 (26.0)			
≥G2	45 (88.2)	151 (74.0)	0.38 (0.1 to 0.9)	0.31 (0.1 to 0.9)	0.038*
1 st gestational age of hypertension					
<37 weeks	34 (66.7)	84 (41.2)			
≥37 weeks	17 (33.3)	120 (58.8)	2.85 (1.5 to 5.4)	1.63 (0.7 to 3.7)	0.241
BMI at delivery period					
≥25 kg/m ²	50 (98.0)	181 (88.7)			
<25 kg/m ²	1 (2.0)	23 (11.3)	0.15 (0.0 to 1.2)	0.12 (0.0 to 1.1)	0.065
1 st high BP level					
>180/120 mmHg	26 (51.0)	51 (25.0)			
160/110 to 180/120 mmHg	25 (49.0)	153 (75.0)	0.32 (0.2 to 0.6)	0.06 (0.0 to 0.2)	<0.001*
Number of antenatal care visits					
<8	18 (35.3)	43 (21.1)			
≥8	33 (64.7)	161 (78.9)	2.04 (1.0 to 4.0)	5.05 (2.0 to 12.4)	<0.001*
Gestational DM					
Yes	17 (33.3)	31 (15.2)			
No	34 (66.7)	173 (84.8)	2.79 (1.4 to 5.6)	2.85 (1.1 to 7.3)	0.029*
Route of delivery					
Spontaneous vertex delivery	11 (21.6)	75 (36.8)			
Cesarean section	40 (78.4)	129 (63.2)	0.47 (0.2 to 1.0)	0.86 (0.3 to 2.1)	0.752
Epigastric pain					
Yes	8 (15.7)	60 (29.4)			
No	43 (84.3)	144 (70.6)	0.44 (0.2 to 1.0)	0.02 (0.0 to 0.1)	<0.001*
Headache					
Yes	14 (27.5)	30 (14.7)			
No	37 (72.5)	174 (85.3)	2.19 (1.0 to 4.5)	2.61 (0.6 to 11.0)	0.193

PE=pulmonary edema; SPIH=severe pregnancy induce hypertension; BMI=body mass index; BP=blood pressure; DM=diabetes mellitus; OR=odds ratio; CI=confidence interval

* Statistically significant

of 105.01±10.28 mmHg, and a mean birth weight of 2,682.76±775.60 grams.

Table 2 presents the maternal characteristics of pulmonary edema in severe preeclamptic women, using bivariate data analysis. Among severe preeclamptic women, the associated factors for pulmonary edema increased 3.75 (95% CI 1.2 to 11.7) times with previous severe pre-eclampsia. The associated factors for pulmonary edema decreased 62% (95% CI 0.1 to 0.9) with nulliparous, increased 2.85 (95% CI 1.5 to 5.4) times with the first gestational age of hypertension less than 37 weeks, decreased 85% (95% CI 0.0 to 1.2) with body mass index (BMI) at delivery period more than 25 kg/m², decreased 68% (95% CI 0.2 to 0.6) with the first high blood pressure

level more than 180/120 mmHg, increased 2.04 (95% CI 1.0 to 4.0) times with the number of antenatal care visits less than eight times, increased 2.79 (95% CI 1.4 to 5.6) times with gestational diabetes mellitus, and decreased 53% (95% CI 0.2 to 1.0) with outcome of birth by cesarean section. The associated factors for pulmonary edema decreased 56% (95% CI 0.2 to 1.0) with epigastric pain and increased 2.19 (95% CI 1.0 to 4.5) times with headache.

Table 3 presents the maternal characteristics of pulmonary edema (PE) in severe preeclamptic women, using multiple logistic regression data analysis. Among severe preeclamptic women, the associated factors for pulmonary edema decreased 69% (95% CI 0.1 to 0.9) with nulliparous, decreased

88% (95% CI 0.0 to 1.1) with the first blood pressure level more than 180/120 mmHg, decreased 98% (95% CI 0.0 to 0.1) with epigastric pain as presenting symptoms. However, the associated factors for pulmonary edema increased 2.04 (95% CI 1.0 to 4.0) times with antenatal care visits of less than eight times and increased 2.79 (95% CI 1.4 to 5.6) times with gestational diabetes mellitus.

Discussion

The present study provides a clinical assessment of the factors associated with pulmonary edema among severe pre-eclamptic women, a case-control study of racially homogeneous women at a single tertiary care referral hospital. All physicians in Pattani Province use the same Pattani clinical practice guidelines based on the guidelines of the Royal College of Obstetricians and Gynecologists of Thailand for diagnosing and treating pre-eclampsia with or without pulmonary edema. The present study found that pulmonary edema developed in 12.75% of the severe pre-eclamptic women in this period, which is higher than the average previously studied because some pregnant women at risk of pre-eclampsia did not attend prenatal care as scheduled until the day they give birth. Moreover, gestational diabetes, which is one of the common risks of pre-eclampsia, was found in 40% to 60% of all pregnant women, with about 10% having poor control blood sugar level, which mostly results in pre-eclampsia along with pulmonary edema. Not only nulliparous but also the first high blood pressure level of more than 180/120 mmHg, epigastric pain as presenting symptoms, number of antenatal cares of less than eight visits, and gestational diabetes mellitus are associated with pulmonary edema among severe pre-eclamptic women.

The authors found that nulliparous severe pre-eclamptic women was an associated factor that decreased the development of pulmonary edema. This result is not consistent with the previous reports^(2,3,12) and can be explained that the quantitative setting of the diagnosis of severe pre-eclampsia with nulliparous in the present study was lower than multiparous. The first of high blood pressure level of more than 180/120 mmHg and presenting symptoms of epigastric pain were lower associated factors to developed pulmonary edema among severe preeclamptic women. This result is not consistent with the previous reports⁽¹³⁾. When the authors first admitted patients who had hypertensive crisis and had important presenting symptoms such as

epigastric pain, they provided emergency and timely treatment including intravenous antihypertensive drugs, MgSO₄ administration, and closed continuous monitoring, all help reduce the development of pulmonary edema.

Gestational diabetes mellitus is highly associated with pulmonary edema among severe pre-eclamptic women. To the best of the authors' knowledge, the authors' study is the only study that evaluated these factors, which not studied in the past. The authors knew that gestational diabetes mellitus is a pregnancy condition with a high risk of pre-eclampsia and may lead to the development of pulmonary edema more often than in pregnant women without gestational diabetes mellitus. The same was true for less than eight antenatal care visits according to Thailand's criteria. This inevitably causes a delay in the evaluation of high blood pressure during pregnancy and leads to a delay in the diagnosis and treatment of pre-eclampsia, leading to more complications of pulmonary edema.

The present study makes it possible to more clearly monitor the factors associated with pulmonary edema in Thai people, which are different from other areas of the world. The results of this present study make it possible to develop the management of severe pre-eclampsia more closely in line with the local context. The present study helps initiate care for gestational diabetes so that blood sugar levels can be controlled within appropriate limits. Because gestational diabetes is one factor that increases the risk of pulmonary edema among severe pre-eclamptic women, emphasis on early prenatal care and at least eight prenatal care visits according to the criteria will help reduce the occurrence of factors associated with the development of pulmonary edema as well.

The present study did not find any severe pre-eclamptic women with pulmonary edema who required further treatment in the intensive care unit, due to timely diagnosis and administration of antihypertensive medication, MgSO₄, oxygenation, and diuretics. Monitoring intravenous fluid administration is an important factor that must be appropriately limited when diagnosing pulmonary edema. The average length of hospital stay for such pregnant women was not more than five days after delivery. The average Apgar score of all newborns was at a safe level and no abnormalities or morbidities were found in the newborns.

The present study was limited by retrospective studies that resulted in incomplete information and

variation in treatment, so a prospective study for these should be performed.

Results from the present study can be used for implementation in the prevention of pulmonary edema found in association with pre-eclampsia as follows, 1) organize a system for following up of high-risk pregnant women to attend the prenatal care at every appointment, 2) control blood sugar levels in the gestational diabetes pregnant women by controlling diet or adjusting blood sugar lowering medication appropriately, 3) physicians decide to give antihypertensive medication early even though blood pressure was in the range of 160/110 to 180/120 mmHg. Future research should focus on preventive methods that may reduce the likelihood of pulmonary edema development. Pulmonary edema in severe pre-eclamptic pregnant women requires early diagnosis and treatment.

Conclusion

The present study found that the prevalence of pulmonary edema among severe pre-eclamptic women was 12.75%. The factors associated with pulmonary edema among severe pre-eclamptic women included gestational diabetes mellitus and poor antenatal care of less than eight visits.

What is already known on this topic?

The previous studies have found that nulliparous pre-eclamptic women are at higher risk of developing pulmonary edema, which is an uncommon complication.

What does this study add?

Early, and regular prenatal care or well-controlling blood sugar levels in women with gestational diabetes mellitus should be implemented for proactive work to reduce pulmonary edema among severe pre-eclamptic women.

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Conflicts of interest

The authors declare no conflict of interest.

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