<Case Report>

Successful Continuation of an At-Risk Pregnancy Secondary to Severe Pulmonary Embolism

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ABSTRACT

We report the case of a 36-year-old pregnant woman who developed severe pulmonary embolism (PE) at 11 weeks of gestation. Despite prompt initiation of anticoagulation therapy, her condition deteriorated with worsening right heart dysfunction. Through meticulous management and multidisciplinary team collaboration, the pregnancy was successfully sustained, and a healthy infant was delivered safely at 37 weeks. This case highlights the clinical importance of early diagnostic imaging, careful adjustment of anticoagulation therapy, and multidisciplinary decision-making in pregnancy-associated PE. In particular, this case suggests that reduced antithrombin III activity may complicate unfractionated heparin therapy.

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INTRODUCTION

Pregnancy is a risk factor for venous thromboembolism (VTE), since it incorporates two components of Virchow's triad, which describes the primary factors contributing to thrombosis: blood flow stasis and a hypercoagulable state [1, 2]. VTE during pregnancy has serious implications in terms of both maternal and fetal outcomes. The risk of VTE is 4–5-fold higher in pregnant women compared to non-pregnant women, and the risk is even higher (20–60-fold) in the postpartum period [3–5]. In fact, pulmonary embolism (PE) accounts for 1.1 deaths per 100,000 deliveries, representing more than 10 % of all maternal fatalities [6–8]. The treatment decisions of PE in pregnancy are particularly challenging due to the limited availability of medication because of concerns regarding teratogenicity and the increased risk of bleeding associated with anticoagulant therapies [9–11]. We present a case of acute PE during early pregnancy in which right ventricular dysfunction progressed despite initial anticoagulation therapy.

CASE PRESENTATION

The patient was a 36-year-old woman at 11 weeks and 1 day of gestation, with a history of two pregnancies and one delivery. She had no past or family history of VTE. One week prior to hospitalization, she presented to her primary care physician with worsening left back pain, leading to hospitalization with a diagnosis of pyelonephritis. She was transferred to our hospital the next day, following the development of sudden respiratory distress.

The patient presented with the following clinical parameters at admission: low-grade fever, a body mass index of 33 kg/m^2, blood pressure: 115/80 mmHg, heart rate: 116 beats/min with regular rhythm, respiratory rate: 28 breaths/min, and oxygen saturation: 94 % under 4 L oxygen via a face mask. Cardiac and respiratory auscultation findings were unremarkable. She had jugular vein distension and bilateral leg edema, but no cyanosis. Her laboratory data showed increased D-dimer, brain natriuretic peptide (BNP) and troponin-I levels (**Table 1**).

Antithrombin III (ATIII), protein C and protein S levels were low at admission. However, since these values normalized at re-evaluation about 1 year later, they were retrospectively judged to be physiological changes related to pregnancy. Her electrocardiogram showed sinus tachycardia and the SIQIIITIII pattern (**Figure 1**). Transthoracic echocardiogram (TTE) showed right ventricular dilatation with moderate tricuspid regurgitation (pressure gradient: 52.2 mmHg) and deformation of the left ventricle (**Figure 2**). Chest X-ray showed cardiomegaly and an area of infiltration in the left lower lung field. Because PE was clinically suspected, contrast-enhanced computed tomography (CT) was performed after careful consideration of the maternal benefit and fetal risk. Contrast-enhanced CT was performed from the neck to the ankles using 95 mL of iohexol 350. Abdominal shielding was not used. The CT scan revealed an enlarged right ventricle and multiple thrombi in both pulmonary arteries (**Figure 3**). Based on right ventricular dysfunction and elevated cardiac biomarkers without persistent hypotension at presentation, she was diagnosed with intermediate-high-risk PE according to guideline-based risk stratification. Anticoagulation therapy was initiated with unfractionated heparin (UFH), consisting

Table 1 Laboratory data on admission

White blood cell	13,750/μL	BNP	165.8 pg/mL
Red blood cell	3.69 × 10^6/μL	Troponin I	301.8 pg/mL
Hemoglobin	11.1 g/dL	PT-INR	1.61
Hematocrit	32 %	aPTT	106.6 s
Platelet	143 × 10^3/μL	Fibrinogen	513 mg/dL
T-Bil	0.8 mg/dL	D-dimer	11.5 μg/mL
AST	21 U/L	Antithrombin III (ATIII)	69 %
ALT	21 U/L	Protein C activity	43 %
LDH	229 U/L	Protein S activity	36 %
BUN	6 mg/dL	Lupus anticoagulant	1.3
Cr	0.48 mg/dL	Anticardiolipin antibody	< 4.0 U/mL
Na	136 mmol/L	Antinuclear antibody	< 40
K	3.4 mmol/L	Anti-dsDNA antibody	< 1.2 IU/mL
CRP	10.7 mg/dL	SARS-CoV-2	negative

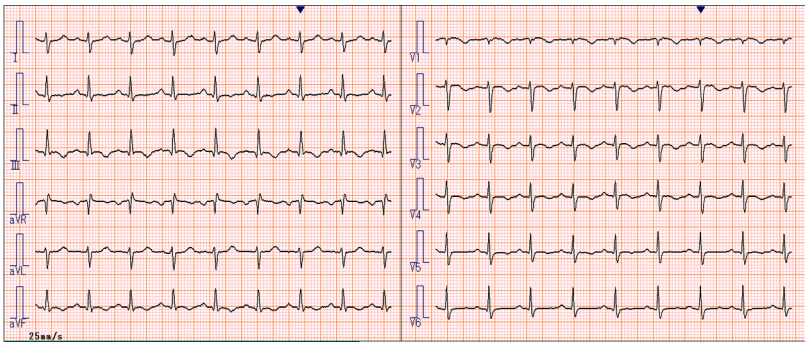
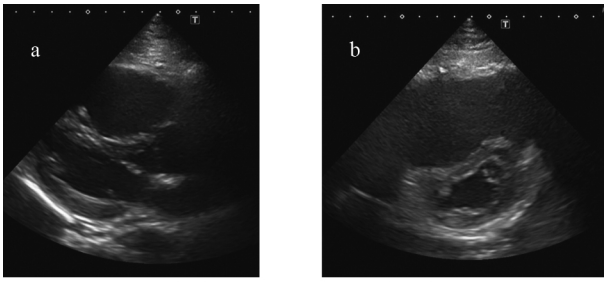


Figure 1 **Electrocardiogram on admission**
Sinus tachycardia and SIQIIITIII pattern were demonstrated on admission.



Parasternal long-axis image　　Parasternal short-axis image

Figure 2 **Transthoracic echocardiogram (TTE) on admission**
a: TTE in parasternal long-axis image
b: TTE in parasternal short-axis image
TTE on admission demonstrated right ventricular dilatation in the parasternal long-axis view and left ventricular D-shape in the parasternal short-axis image.

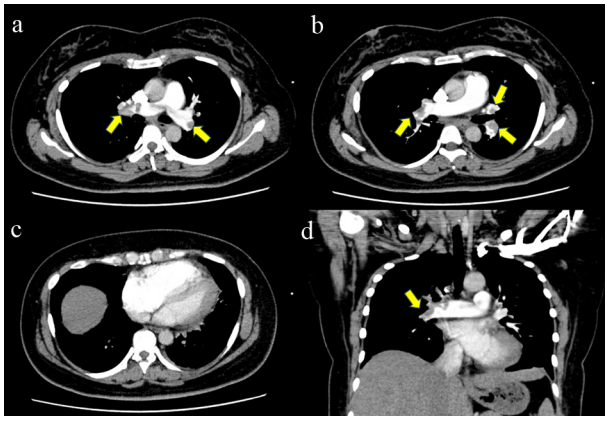


Figure 3 **Contrast-enhanced chest computed tomography on admission**
a: axial section in the bifurcation level of the pulmonary artery
b: axial section in the main trunk level of the pulmonary artery
c: axial section in both ventricular levels
d: coronal section in the right pulmonary artery level
Contrast-enhanced CT revealed right ventricular enlargement and multiple thrombi in both pulmonary arteries, indicated by yellow arrowheads.

of a 5,000 U intravenous bolus followed by continuous infusion at 20,000 U/day. The target activated partial thromboplastin time (aPTT) range was set at 50–80 seconds. The UFH dose was subsequently adjusted according to aPTT values and clinical status. The clinical course of anticoagulation therapy, including UFH dose, aPTT, D-dimer, ATIII activity, ATIII supplementation, symptoms, and ICU admission status, is summarized in **Figure 4**.

On the 4th day of hospitalization, the dyspnea temporarily improved in the morning, but worsened later that evening with the sudden onset of chest pain and respiratory distress. Subsequently, her blood pressure decreased to 89/54 mmHg and oxygen saturation declined to 88 % despite receiving 10 L oxygen via a face mask. Because she developed hypotension, worsening hypoxemia, and progressive right ventricular compromise, her condition was reclassified as high-risk PE. At this time, despite UFH therapy, D-dimer increased again to 22.1 μg/mL, and ATIII activity decreased to 56 %. The platelet count was 143,000/μL at admission and 140,000/μL at clinical deterioration, and subsequently remained approximately 150,000–200,000/μL until delivery. HIT was excluded because the HIT antibody was negative.

In this case, since pregnancy was considered a major predisposing and exacerbating factor for VTE, continuing pregnancy was potentially dangerous for both mother and fetus. At a multidisciplinary team conference held to discuss the management of this patient, the obstetrician emphasized the need to consider both maternal and fetal safety, including the possibility of pregnancy termination if maternal hemodynamics could not be stabilized. The pharmacist explained that reduced ATIII activity may attenuate the anticoagulant effect of UFH. Because ATIII activity was reduced and insufficient anticoagulant response to UFH was suspected,

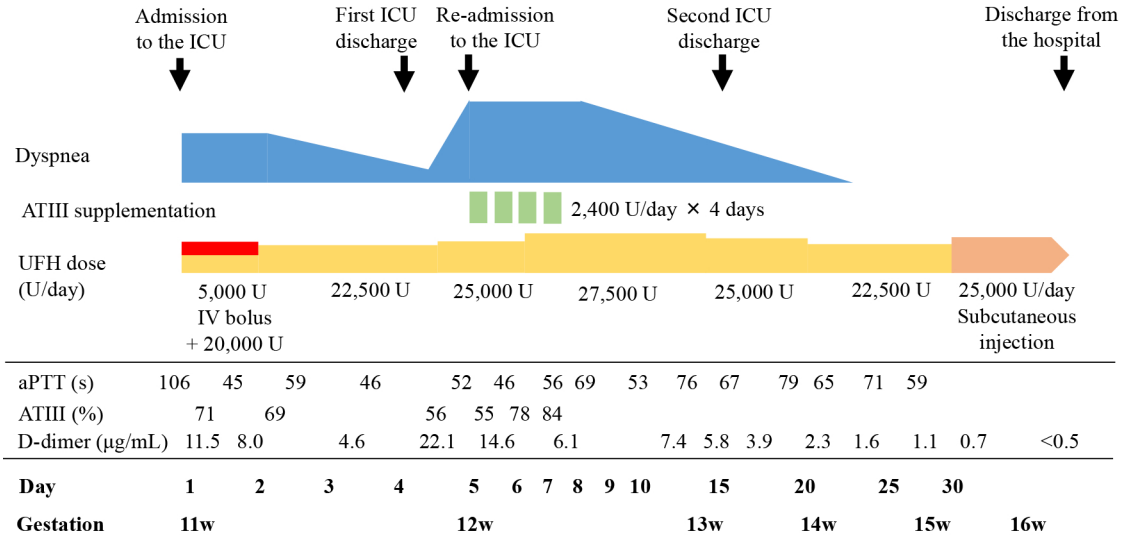


Figure 4 **Clinical course of anticoagulation therapy**
The figure shows the changes in aPTT, D-dimer, ATIII activity, UFH dose, ATIII supplementation, symptoms, and ICU admission status from Day 1 to Day 30. The target aPTT range was 50–80 seconds. ATIII activity decreased to 56 % and subsequently to 55 % around clinical deterioration and increased after ATIII supplementation. aPTT: activated partial thromboplastin time; ATIII: antithrombin III; ICU: intensive care unit; UFH: unfractionated heparin.

ATIII supplementation was considered. Since ATIII activity measured at symptom exacerbation was low at 56 % and subsequently decreased to 55 % (normal range, 80–120 %), ATIII supplementation was administered at 2,400 U/day for 4 days. From a pharmaceutical perspective, a recombinant ATIII product was selected instead of a plasma-derived ATIII product, considering the potential infection risk associated with biological products. After ATIII supplementation, ATIII activity increased to 78 % and 84 %, and aPTT remained within or near the target range with UFH dose adjustment. Her dyspnea and chest pain improved. Bedside transthoracic echocardiography was performed daily during the acute phase. Stored echocardiographic images were available on Day 1, Day 5, Day 12, and Day 18. On Day 1 and Day 5, right ventricular enlargement with left ventricular compression was observed, suggesting pulmonary hypertension and right ventricular pressure overload. On Day 12 and Day 18, left ventricular compression had disappeared, suggesting improvement in pulmonary hypertension and right ventricular pressure overload (**Figure 5**). Repeat contrast-enhanced CT was not performed because of clinical stabilization and concern regarding fetal radiation exposure. Anti-Xa activity was not measured during the patient's hospital stay. We decided to continue the pregnancy. After stabilization, the patient was switched from continuous UFH infusion to subcutaneous heparin calcium administered twice daily at a total dose of 25,000 U/day and was discharged on the 30th hospital day. Fetal heart tones were confirmed by abdominal ultrasonography on Day 1

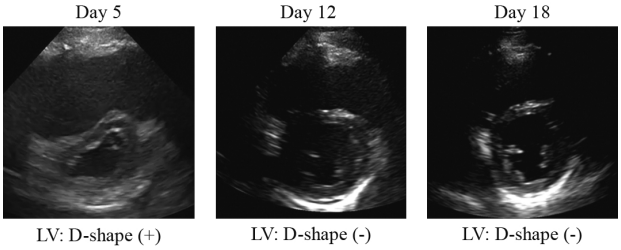


Figure 5 **Serial echocardiographic changes in right ventricular pressure overload**
Representative echocardiographic images are shown. Left ventricular D-shape, suggesting right ventricular pressure overload and pulmonary hypertension, was observed on Day 1 and Day 5. The D-shape had disappeared on Day 12 and Day 18, suggesting improvement in right ventricular pressure overload. Day 1 corresponds to the echocardiographic examination performed on admission.

and Day 14. The pregnancy was successfully continued, and cesarean delivery was performed at 37 weeks of gestation because of breech presentation. A healthy infant weighing 3,190 g was delivered, with Apgar scores of 8 and 10 at 1 and 5 minutes, respectively. The infant did not require neonatal intensive care unit admission. Both the mother and infant had an uneventful postpartum course and were discharged 1 week after delivery.

For peripartum anticoagulation management, subcuta-

neous heparin was switched to continuous intravenous UFH after admission for delivery. UFH was discontinued 9 hours before cesarean delivery and restarted 12 hours after delivery. After delivery, warfarin was initiated during hospitalization at 5 mg/day. After PT-INR prolongation (PT-INR 1.8–1.9) was confirmed, the dose was adjusted to 2.5–3 mg/day before discharge. Considering the high risk of postpartum VTE, warfarin therapy was continued until 6 weeks postpartum. No recurrent VTE events were observed after first discharge. No bleeding complications related to anticoagulation therapy were observed during hospitalization, after discharge, at delivery, or during the postpartum period.

DISCUSSION

Epidemiology of VTE in Pregnancy

The risk of VTE during pregnancy is almost 6 times higher than in the general population, with an absolute risk of 12.2 per 10,000, compared with 2 per 10,000 in non-pregnant women [12]. The risk of VTE also increases with gestational age, peaking during the first 2 postpartum weeks. Compared to non-pregnant women, the risk of VTE is more than 2-fold higher in the first and second trimesters, 9-fold higher in the third trimester and 80-fold higher in the first 2–6 postpartum weeks [13, 14]. PE in pregnant women is frequently observed during the postpartum period after cesarean section. Current data indicate that in developed countries, from 11 % to 24 % of pregnancies culminate in a cesarean section. Being an invasive procedure, cesarean sections are associated with a 4.9-fold increased risk of VTE compared to vaginal delivery [12]. In this case, several factors, including pregnancy, obesity, infection, and possible reduction in physical activity during hospitalization for suspected pyelonephritis, may have contributed to thrombus formation. However, the causal contribution of urinary tract infection alone cannot be determined.

Difficulty and Importance of Early Diagnosis of VTE in Pregnancy

Diagnosing VTE during pregnancy can be challenging [15], since its typical symptoms, shortness of breath and leg swelling, can mimic symptoms commonly associated with normal pregnancy. The presence of PE in pregnant women should be suspected if shortness of breath persists even at rest or occurs with mild exertion. Unilateral swelling, persistent edema despite limb elevation, or pain on ambulation, which are not typical of normal pregnancy, might suggest the presence of deep vein thrombosis. When clinical signs suggestive of VTE, especially PE, are observed, early diagnosis should be prioritized. In patients with PE during pregnancy, survival reportedly correlates strongly with early diagnosis [16].

Early diagnosis often requires imaging studies, including contrast-enhanced CT. Current guidelines [17] and previous reports indicate that diagnostic imaging should not be withheld when PE is clinically suspected during pregnancy, because delayed diagnosis may worsen maternal prognosis. Although fetal radiation exposure is an important concern, the fetal radiation dose from pulmonary artery CT angiography is generally reported to be below the threshold associated with fetal malformations [18]. Therefore, in clinically suspected maternal PE, contrast-enhanced CT should be considered after careful assessment of maternal benefit and fetal risk.

Anticoagulation therapy and ATIII activity

UFH exerts its anticoagulant effect mainly by enhancing the activity of ATIII [19]. Therefore, reduced ATIII activity may attenuate the anticoagulant effect of UFH and complicate anticoagulation management. In the present case, clinical deterioration occurred despite UFH therapy, and ATIII activity decreased to 56 % and subsequently to 55 % around the time of symptom exacerbation. After ATIII supplementation and UFH dose adjustment, ATIII activity increased and the patient's symptoms and echocardiographic findings improved. However, because anti-Xa activity was not measured and repeat contrast-enhanced CT was not performed after clinical stabilization, the direct effect of ATIII supplementation cannot be definitively proven in this single case. This case suggests that ATIII activity should be considered when the anticoagulant effect of UFH appears insufficient during pregnancy-associated PE.

Management of Severe Cases of PE During Pregnancy

When VTE occurs during pregnancy, the treatment strategies should be carefully tailored to the stage of pregnancy and severity of heart disease. In the case of PE, termination of pregnancy might be considered depending on the PE severity. For patients with normal blood pressure and no evidence of right heart dysfunction, anticoagulant therapy is the preferred treatment. When right heart dysfunction is present, but blood pressure remains normal, anticoagulant therapy should be administered after careful assessment of the risks and benefits. Thrombolytic therapy should also be considered in cases with persistent shock or hypotension [20]. While thrombolytic therapy offers the advantage of rapid thrombus dissolution and improved hemodynamics, it tends to be associated with an increased risk of bleeding complications [21]. In pregnant women, bleeding complications secondary to thrombolytic therapy are of serious concern given their impact on the fetus. Since previous studies have reported high maternal survival rates in pregnant women with severe PE who received thrombolytic therapy, as well as an increased risk of maternal hemorrhage and fetal mortality, the choice of whether or not to administer such therapy should be made cautiously [22, 23]. However, in situations involving persistent shock or hypotension, thrombolytic therapy might be unavoidable. Additionally,

in severe PE cases, early delivery of the fetus should be considered to minimize the risk of postpartum hematoma formation. Premature neonates might require care in the neonatal intensive care unit after birth. Hence, in actual clinical settings, a coordinated response from various specialists is essential, requiring collaboration between obstetricians, neonatologists, and cardiologists at specialized facilities where all relevant medical disciplines are available.

This case also illustrates the importance of multidisciplinary decision-making in severe PE during pregnancy. The cardiology team evaluated maternal hemodynamics and right ventricular dysfunction, the obstetric team assessed the feasibility of pregnancy continuation and fetal condition, and the pharmacy team contributed to optimization of anticoagulation therapy by focusing on the relationship between ATIII activity and UFH efficacy and by selecting a recombinant ATIII product considering the potential infection risk associated with plasma-derived biological products. The midwife and nursing team contributed to close monitoring of maternal symptoms and fetal well-being during the clinical course. Such multidisciplinary information sharing was essential for balancing maternal stabilization and fetal safety.

CONCLUSION

This case illustrates that pregnancy-associated PE can deteriorate rapidly despite initial anticoagulation therapy. Multidisciplinary management, including obstetric and pharmaceutical perspectives, contributed to adjustment of anticoagulation therapy and continuation of pregnancy. This case suggests that ATIII activity may be an important consideration when UFH appears insufficiently effective in severe pregnancy-associated PE.

ETHICS STATEMENT

Written informed consent for publication of this case report and accompanying images was obtained from the patient.

DISCLOSURE STATEMENT

The authors state that they have no Conflict of Interest (COI).

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