JACC: CASE REPORTS VOL. 2, NO. 12, 2020

MINI-FOCUS ISSUE: INTERVENTIONAL CARDIOLOGY

INTERMEDIATE

CASE REPORT: CLINICAL CASE

Catheter-Directed Thrombolysis for Submassive Pulmonary Embolism in the Third Trimester of Pregnancy

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ABSTRACT

A 37-year-old woman presented with chest pain and shortness of breath in the third trimester of pregnancy. Diagnostic imaging demonstrated a saddle pulmonary embolism, severe impairment of right ventricular function, and an extensive deep venous thrombus. She underwent catheter-directed thrombolysis with tissue plasminogen activator and delivered a healthy infant at term. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:1899-904)

PRESENTATION

A 37-year-old nullipara presented to the emergency department at 33 weeks 2 days gestational age with several hours of shortness of breath and chest pain. Initial evaluation was notable for tachycardia to 120 beats/min, tachypnea with a respiratory rate of 30 breaths/min, and oxygen desaturation requiring 4 liters of supplemental oxygen through high-flow nasal cannula to maintain saturations above 94%. Blood pressure was normal at 112/70 mm Hg. She was dyspneic at rest and became increasingly dyspneic with speaking. On examination, jugular venous pressure was elevated to 6 cm above the sternal angle, and a right ventricle (RV) heave was palpated. Heart sounds S1 and S2 were normal, without accentuation of S2. S2 was not palpable. Breath sounds were decreased bilaterally, and asymmetrical swelling of the right lower extremity was present.

LEARNING OBJECTIVES

- To describe unique considerations for treatment of a pulmonary embolism in pregnancy.
- To illustrate a novel way of treating a submassive pulmonary embolism in pregnancy.
- To review the published medical literature surrounding the use of catheter-directed thrombolysis for treatment of pulmonary embolism in pregnancy.

MEDICAL HISTORY

The patient had been found to be heterozygous for the prothrombin gene mutation G20210A 2 years prior on elective carrier screening. She also had a recent

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received March 30, 2020; revised manuscript received July 16, 2020, accepted August 13, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.08.022

ABBREVIATIONS AND ACRONYMS

CDT = catheter-directed thrombolysis

CTA = computed tomography angiography

IV = intravenous

PA = pulmonary artery

PE = pulmonary embolism

POD = post-operative day

RV = right ventricle

UFH = unfractionated heparin

history of immobility after a soft tissue injury of the right knee 2 weeks prior to presentation. She denied any other medical history.

DIFFERENTIAL DIAGNOSIS

Given her history, symptoms, and vital sign abnormalities, differential diagnosis included pulmonary embolism, cardiac arrhythmia, undiagnosed cardiac structural abnormality, pregnancy-related cardiomyopathy, and infectious causes such as pneumonia with pleurisy or pleural effusion and pericarditis.

INVESTIGATIONS

The patient's laboratory results were notable for a hemoglobin of 11.1 g/dl, white blood cell count of 10.1×10^9 l; and platelet count of 175×10^9 l. Her serum lactate was 0.9 mmol/l. Her initial troponin was 0.48 ng/ml (reference range: <0.05 ng/l). Electrocardiography showed sinus tachycardia. There was high suspicion for pulmonary embolism with concern for impending hemodynamic instability based on vital signs and physical examination findings. Thus, the decision was made to forego lower extremity Doppler ultrasonography as the initial study and to proceed directly to computed tomography angiography (CTA). The benefit of reaching a prompt diagnosis and rapid initiation of treatment was thought to outweigh the minimal risks of radiation to the fetus, and the patient was amenable to this treatment. Of note, the fetal radiation exposure associated with CTA is estimated at a maximum of 0.66 mGy, which is well below the 50-mGy threshold of increased risk of intrauterine fetal demise, fetal growth restriction, and significant adverse neurodevelopmental outcomes (1).

CTA with intravenous (IV) iohexol (Omnipaque 350, GE Healthcare, Chicago, Illinois) in a solution of 100 ml with abdominal shielding was performed and demonstrated a saddle pulmonary embolism (PE) (**Figure 1**). Transthoracic echocardiography demonstrated a flattened interventricular septum in diastole, consistent with RV volume overload, an elevated estimated systolic pulmonary artery (PA) pressure of 46 mm Hg and thrombus in the main PA and PA branches (**Figure 2**). Lower extremity Doppler ultrasonography demonstrated an extensive, occlusive, right-sided deep venous thrombosis extending from the popliteal vein up to the femoral vein.

MANAGEMENT

Following the results of the CTA, IV unfractionated heparin (UFH) was initiated. The patient's clinical status was reviewed by a multidisciplinary team including specialists in maternal fetal medicine, cardiology, obstetric anesthesia, interventional radiology, and critical care. Based on the patient's worsening tachycardia, tachypnea, and oxygen requirement and increasing troponin concentrations (to 0.51 μg/l) over 18 h of IV UFH treatment, the multidisciplinary team expressed concern for impending hemodynamic instability. Re-evaluation for clinical improvement after 24 to 48 h of IV UFH was deemed imprudent due to the potential for rapid deterioration in maternal status that would prompt emergent delivery and resuscitation, which would be catastrophic in the setting of RV dysfunction.

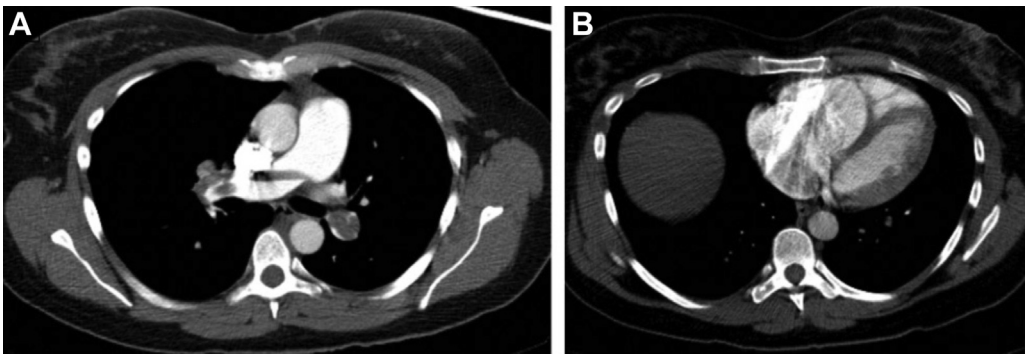
In the setting of the large clot in the main PA, evidence of severe RV dysfunction, and concern for worsening cardiac status during 6 additional weeks of pregnancy, followed by delivery, catheter-directed thrombolysis (CDT) using tissue plasminogen activator was recommended. The recommendation was also made for an inferior vena cava filter placement, due to the significant lower extremity clot burden and the need to discontinue anticoagulation during delivery. The multidisciplinary members shared their decisions with the patient, with careful consideration of the risks, benefits, and alternatives to this therapy, included continuing UFH for at least 24 to 48 h. The team discussed the fact that CDT could help remove clot burden and allow for improvement in RV function before her anticipated delivery in 6 weeks.

The team also discussed the fact that the maternal and fetal risks associated with this intervention were hard to calculate, given the limited available medical literature regarding use of CDT in pregnancy but that the few case reports in pregnancy had favorable outcomes. The fetal risk of radiation exposure with CDT and inferior vena cava filter placement were also reviewed, which is considered low in the third trimester and outweighed by the maternal benefits (1).

Following appropriate patient counseling and informed consent, bilateral ultrasonography-assisted thrombolysis catheters and suprarenal inferior vena cava filter were placed in the interventional radiology suite (**Figure 3**). IV iohexol 350 in a solution of 50 ml was used during fluoroscopy. Tissue plasminogen activator was infused at a rate of 1.0 mg/h along with UFH through the ultrasonography-assisted thrombolysis catheters for 24 h while the patient remained in the intensive care unit for close monitoring and continuation of IV UFH. Continuous electronic fetal heart rate monitoring was performed during this time.

On post-operative day (POD) 1, ultrasonography-assisted thrombolysis catheters were removed,

FIGURE 1 Chest Computed Tomography



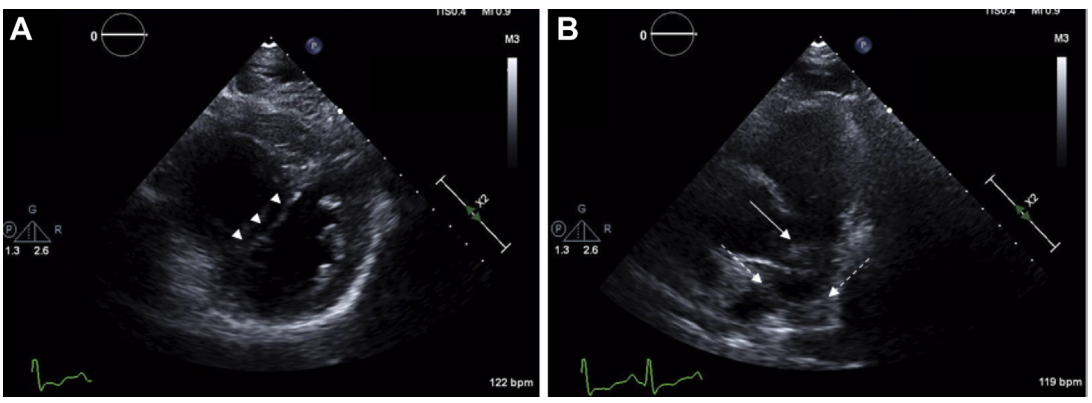
Chest computed tomography shows **(A)** axial image of saddle pulmonary embolus and **(B)** right ventricular dilation with right-to-left ventricle diameter (RV/LV) ratio >1.

with improvement in RV size and function and troponin decrease to 0.35 ng/ml. By POD 2, the patient was able to maintain saturations ≥99% on room air. Subcutaneous low-molecular-weight heparin was initiated on POD 2, with a target peak concentration of 0.8 to 1.2 U/ml and a trough concentration >0.6 U/ml to avoid supratherapeutic and subtherapeutic effects, respectively. On POD 3, transthoracic echocardiography demonstrated a 12-mm Hg decrease in estimated PA systolic pressure, further indicating hemodynamic improvement. The patient was discharged at 34 weeks 2 days gestation with a plan for close outpatient follow-up. Fetal monitoring throughout her hospital admission was reassuring.

DISCUSSION

PE is one of the leading causes of maternal morbidity and mortality in the United States, accounting for 9.5% of pregnancy-related deaths from 2008 to 2017 (2). The hypercoagulable state of pregnancy increases the risk of venous thromboembolism 4-fold above the general population, for an overall venous thromboembolism incidence of 0.5 to 2 per 1,000 pregnancies (3). Inherited thrombophilias increase the risk of venous thromboembolism in pregnancy; for example, the prothrombin G20210A mutation is associated with a 2- to 3-fold increased risk of venous thromboembolism (4). However, the overall risk of venous thromboembolism in pregnancy remains <1% for a

FIGURE 2 Transthoracic Echocardiogram



Transthoracic echocardiogram shows **(A)** flattening of interventricular septum **(arrowheads)** during diastole, consistent with right ventricular volume overload, and **(B)** visible thrombus in the main pulmonary artery **(solid arrow)** and pulmonary artery branches **(dashed arrows)**.

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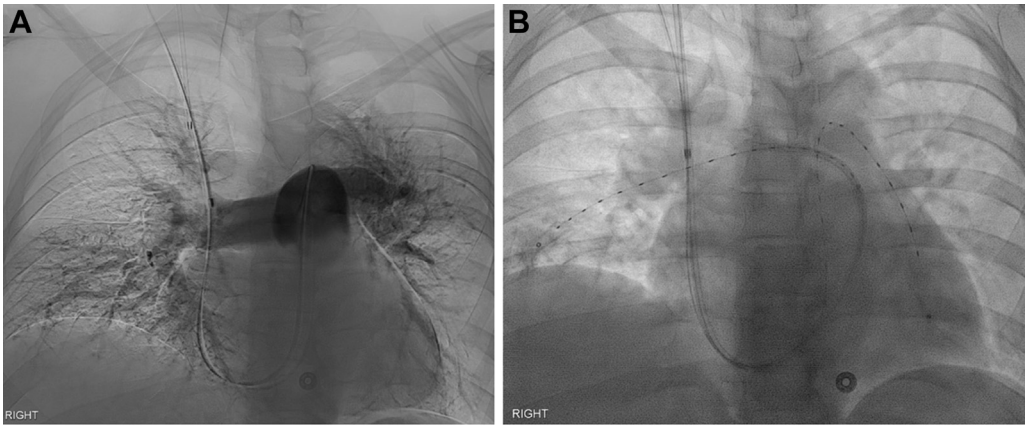
FIGURE 3 Pulmonary Angiogram



Pulmonary angiogram demonstrates **(A)** saddle pulmonary embolus with bilateral peripheral filling defects and **(B)** bilateral ultrasonography-assisted thrombolysis catheters in the lower lobe of the pulmonary arteries.

prothrombin gene heterozygote with no history of venous thromboembolism, thus, the standard practice is to not initiate anticoagulation in these patients in pregnancy.

When a pregnant patient does receive a diagnosis of venous thromboembolism, the standard treatment for PE in pregnancy is systemic anticoagulation, regardless of PE classification (3). In the nonpregnant population, however, treatment varies based on PE classification (5). Despite the lack of high-quality data to support its use, thrombolytic therapy for PE in pregnancy has been documented in a handful of case reports and observational studies.

In the present case, CDT is described as the first-line treatment for a submassive PE in the third trimester of pregnancy. Because there are currently no guidelines regarding thrombolysis for PE in pregnancy, providers interested in using this treatment must extrapolate from data in the nonpregnant population. According to the 2016 guidelines from the American College of Chest physicians, systemic thrombolytic therapy is recommended only for patients with a massive PE and for patients with a submassive PE who clinically deteriorate despite systemic anticoagulation (6). There is currently no consensus surrounding the use of systemic or catheter direct thrombolysis as a primary treatment for patients who present with a submassive PE, due to controversy regarding risk-benefit ratio. Compared to systemic thrombolysis, CDT has the potential to lower the risk of bleeding by localizing drug delivery directly to the area of interest, allowing for a two-thirds reduction in the required dose (7). Numerous studies have demonstrated the efficacy and safety of CDT for PE in the general population. For example, 2 prospective observational studies each with 100 patients demonstrated significant reduction in right ventricle-to-left ventricle (RV/LV) ratios, significant improvement in PA pressures, and 80% clinical success rate when using CDT for massive and submassive PEs (5). A third prospective study was a randomized controlled trial that demonstrated more rapid normalization of the RV/LV ratio with CDT compared to UFH in patients with a submassive PE (5). The overall bleeding rates in these 3 studies were low, with only 1 severe incidence of bleeding and 16 moderate incidences of bleeding in a total of 280 cases. Although these studies demonstrate the efficacy and safety of CDT, there have been no direct comparisons of CDT to systemic thrombolysis. As such, the most recent CHEST guidelines recommend reserving CDT for cases with a particularly high risk of bleeding (6).

Whether thrombolysis should be used in pregnancy, whether thrombolysis should be used in submassive PEs in all subjects, and whether thrombolysis should be given systemically or in a catheter-directed fashion are all topics of ongoing debate. Thus, the use of CDT as first-line treatment for a submassive PE in pregnancy makes the present case a unique situation. In this case, the decision was made based on multidisciplinary discussion among specialty providers and shared with

TABLE 1 5 Previous Case Reports Describing the Use of CDT for PE in Pregnancy

			Maternal Outcome		Fetal/Neonatal Outcome	
First Author, Year (Ref. #)	GA at Diagnosis	Type of PE	Complications	Length of Follow-Up	Complications	Length of Follow-Up
Gowda et al., 2019 (8)	9 weeks	Massive	Pulmonary infarct	Through delivery	None	Through delivery
Sofocleous et al., 2001 (10)	15 weeks	Massive	Major bleeding*	Through delivery	Fetal demise	N/A
Pick et al., 2015 (11)	33 weeks	Submassive	Pre-eclampsia	Through delivery	PTB	Through delivery
Krishnamurthy et al., 1999 (9)	26 weeks	Massive	None	Through delivery	None	Through delivery
Bechtel et al., 2005 (12)	30 weeks	Massive	None	Through delivery	None	Through delivery

*Source of bleeding was not identified, but the patient became hypotensive and anemic (drop in hemoglobin by 2 g/dl) 24 h after the procedure.
CDT = catheter-directed thrombolysis; GA = gestational age; PE = pulmonary embolus; PTB = preterm birth.

the patient, with careful consideration of the risks, benefits, and alternatives to this therapy, as outlined above. Particular emphasis was given to the interaction between ongoing RV dysfunction and the cardiovascular burden of 6 additional weeks of pregnancy followed by labor and delivery. Pregnancy is a state of increased cardiac output and blood volume, and the normal physiologic changes of pregnancy, labor, and delivery often worsen underlying cardiac dysfunction. The primary concern for this patient was that without thrombolysis, cardiac dysfunction would worsen with ongoing pregnancy, with the potential for catastrophic urgent preterm delivery or decompensation during term delivery. CDT was chosen over systemic thrombolysis to minimize the dose of tissue plasminogen activator, given concerns regarding risk of bleeding and possible fetal effects (7).

This case adds to the limited studies regarding use of CDT in pregnancy. In the review, 5 case reports of CDT were identified for PE in pregnancy (**Table 1**) (8–12). In 1 case of submassive PE, CDT was used only after the patient developed severe RV dysfunction despite therapeutic anticoagulation. There were no maternal complications in any of the cases. In 1 case, an intrauterine fetal demise occurred 1 day after CDT; however, this fetal death was attributed to maternal acuity. None of the prior cases report long-term maternal outcomes.

This is the third case report to describe CDT as treatment for a PE in the third trimester of pregnancy. In any trimester of pregnancy, CDT for massive or submassive PE can be considered for patients with current or impending hemodynamic instability. In the third trimester, special consideration should be given to CDT as the first-line treatment for any submissive PE due to the potential catastrophic events that acute decompensation could prompt, including the need for premature delivery with the myriad of short- and long-term complications of prematurity and the further deterioration of maternal status when the hemodynamic burden of an emergency delivery is superimposed on significant cardiopulmonary dysfunction. Furthermore, given the inherent limitations of gestation, patients in the third trimester have less time for cardiac function to improve before the intense cardiovascular stress of labor and delivery.

FOLLOW-UP. The patient presented at 38 weeks 5 days gestation for a scheduled induction of labor. Low-molecular-weight heparin was discontinued, and IV UFH was initiated, with monitoring of activated partial thromboplastin time. The patient delivered a healthy infant weighing 3,735 g at 39 weeks 0 days gestation. On postpartum day 1, she was transitioned back to weight-based therapeutic low-molecular-weight heparin, with the plan to continue this for 6 months. The remainder of her postpartum course was unremarkable, and she and the infant were discharged home on postpartum day 4. The inferior vena cava filter was removed 2 months postpartum. The filter was kept in place longer than the standard 4-week period due to the unique hypercoagulability of the postpartum state and the patient's extensive lower extremity clot burden. At a follow-up visit 6 months after CDT, the patient was doing well and reported a healthy infant who was meeting all pediatric milestones.

CONCLUSIONS

In summary, this paper describes the case with excellent maternal and neonatal outcome following CDT as first-line treatment for a submassive PE in the third trimester of pregnancy. Further research should explore the efficacy and safety of this treatment in pregnancy. Due to the complex physiologic changes in pregnancy and the cardiovascular strain associated with delivery, pregnant patients in the third trimester with submassive PE may derive the most benefit from

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OCTOBER 2020:1899–904

expeditious thrombolysis and associated resolution right ventricular strain.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEYWORDS catheter-directed thrombolysis, pregnancy, thromboembolism