What to Do When They're Eating for Two? A Case of Catheter-Directed Thrombolysis for Submassive Pulmonary Embolism in Pregnancy

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ABSTRACT

A 33-year-old G7P0 female at 8 weeks gestation presented to the emergency department (ED) following a syncopal episode. She complained of chest pain and dyspnea, and had hemodynamic instability, which responded to intravenous fluids. Continued fluid resuscitation, supplemental oxygen, as well as therapeutic dose low molecular weight heparin (LMWH) were administered in the ED. Computed tomography (CT) pulmonary angiogram confirmed saddle pulmonary embolism (PE). After 12 h of continued chest pain and high oxygen requirements, a decision was made to use catheter-directed thrombolysis (CDT) involving alteplase with manual thrombus maceration in bilateral pulmonary arteries. There were no immediate hemorrhagic complications and follow-up fetal ultrasound demonstrated a normal viable intrauterine pregnancy. She clinically improved and was discharged on LMWH. Cesarean section was scheduled, and the patient delivered a healthy term infant at 37 weeks gestation without complications. Our case demonstrates that CDT may be a safe and effective treatment for submassive PE in pregnancy.

RÉSUMÉ

Une femme âgée de 33 ans et enceinte de huit semaines (G7P0) se présente aux urgences à la suite d'un épisode syncopal. Elle se plaint de douleurs thoraciques et de dyspnée et présente une instabilité hémodynamique qui répond aux solutés intraveineux. Une réanimation liquidienne continue, une oxygénothérapie ainsi qu'une dose thérapeutique d'héparine de faible poids moléculaire sont administrées aux urgences. L'angiographie pulmonaire par tomodensitométrie confirme une embolie pulmonaire en selle. Après 12 heures de douleurs thoraciques continues et de besoins élevés en oxygène, on décide d'utiliser la thrombolyse dirigée par cathéter (TDC) à l'aide de l'altéplase avec macération manuelle du thrombus dans les artères pulmonaires bilatérales. Il n'y a pas eu de complications hémorragiques immédiates et le suivi échographique du fœtus a démontré une grossesse intra utérine normale et viable. Son état clinique s'est amélioré et elle a obtenu son congé sous héparine de faible poids moléculaire. Une césarienne a été planifiée et la patiente a accouché d'un enfant à terme et en bonne santé à 37 semaines de grossesse, sans complications. Notre cas démontre que la TDC peut être un traitement sûr et efficace de l'embolie pulmonaire submassive en cours de grossesse.

Case Report

A 33-year-old female, 8 weeks pregnant (Gravida 7, Para 0), with past medical history significant for hypothyroidism, uterine leiomyomas, and seven spontaneous abortions (all <20 weeks' gestational age) presented to the emergency department (ED) with chest pain, right upper quadrant abdominal pain, and dyspnea. She had reported a brief syncopal episode on ambulation earlier that day. Medications included levothyroxine and prenatal vitamins. Family history was significant for systemic lupus erythematosus (SLE). In the ED, she was neurologically intact, appeared diaphoretic, and had an increased work of breathing. Vital signs demonstrated hypotension (88/66 mmHg), tachycardia (126 beats per minute), and tachypnea (36 breaths per minute). Intravenous fluids were administered with an increase in systolic blood pressure to 100 mmHg, and 100% oxygen by facemask was applied, which improved the hypotension and hypoxia; however, tachycardia persisted.

Initial investigations included an electrocardiogram (ECG) demonstrating sinus tachycardia, S₁Q₃T₃ phenomenon, and evidence of right heart strain (Figure 1). Initial high-sensitivity troponin I was 126 ng/L (normal < 30 ng/L), and bedside point of care ultrasound demonstrated right ventricular (RV) dysfunction. A computed tomography (CT) scan of the thorax demonstrated a pulmonary embolism (PE) with a large clot burden involving distal left and right main pulmonary arteries, and extending into the lobar arteries (Figure 2).

Formal transthoracic echocardiogram demonstrated severe RV enlargement, moderately to severely impaired RV systolic function, and akinesia of the RV free wall. RV systolic pressure (RVSP) was 29 mmHg and left ventricular ejection fraction (LVEF) was 60–65%. The diagnosis of submassive PE was confirmed. Therapeutic dose low molecular weight heparin (LMWH; dalteparin 200 IU/kg = 18,000 IU) was administered subcutaneously, and the patient was transferred to the intensive care unit (ICU). Repeat troponin rose

Figure 1. Electrocardiogram demonstrating S₁Q₃T₃, sinus tachycardia and right heart strain on initial presentation.

Figure 2. CT PE at diagnosis demonstrating the clot burden. CT = computed tomography; PE = pulmonary embolism.

to 1335 ng/L. Despite receiving multiple doses of morphine for analgesia, she continued to complain of abdominal pain, pleuritic chest pain, and dyspnea. Supplemental oxygen was titrated down from FiO₂ 100 to 40% by facemask to maintain SaO₂ above 95%. Blood pressure remained stable at 100–110/80–90 mm Hg.

On subsequent evaluation, her symptoms persisted despite initial treatment with anticoagulants. Weighing the persistence of symptoms in a patient with submassive PE against a low bleeding risk profile, the decision was made to proceed with catheter-directed thrombolysis (CDT). After obtaining informed consent outlining risks of mortality (1%), major bleeding (8–10%), and 5–10% risk of fetal loss, she underwent CDT on day one of her hospital admission. Through a 5F vascular sheath in the right common femoral vein, 5 mg of tissue plasminogen activator (tPA; Alteplase) was laced in each main pulmonary artery (total bolus of 10 mg) via a 5F pigtail catheter. The tPA sat within the thrombus for 5 min, followed by manual maceration of the thrombus. The pigtail was then pulled back into the main pulmonary artery for continuous tPA infusion of 1 mg/h (0.01 mg/h at 100 mL/h). Heparin was simultaneously infused at 500 IU/h (40 IU/mL at 12.5 mL/h) via the right common femoral vein sheath to prevent thrombus formation on the catheter and provide subtherapeutic anticoagulation. Efforts were made to limit the radiation dose to the fetus during the procedure by minimizing the angiographic runs, appropriate collimation, and decreasing the pulse rate of fluoroscopy to 2–3 pulses per second. After 7 h of tPA infusion, there was marked clinical improvement, with FiO₂ requirements decreasing to 4L/min by nasal prongs, heart rate decreasing to 112 bpm, and resolution of the chest pain and dyspnea. The tPA infusion was discontinued, the catheter and sheath were removed

and a therapeutic heparin infusion was initiated. There were no hemorrhagic complications. Symptoms of chest and abdominal pain resolved, and supplemental oxygen was discontinued. Fetal ultrasound on day 3 of admission demonstrated a single viable intrauterine pregnancy. Given the patient's history of recurrent pregnancy loss, antiphospholipid antibody testing was ordered and returned negative (anti-cardiolipin IgG and beta2-glycoprotein IgG both < 5 units/mL), which supported the belief that her previous fetal losses were secondary to leiomyomas. She was transitioned to tinzaparin 18,000 IU SC daily and discharged home 7 days after her initial presentation with close follow-up arranged.

She was followed throughout her pregnancy where she continued to be asymptomatic with no episodes of major bleeding, recurrent venous thromboembolism (VTE), or pregnancy complications. She remained on tinzaparin throughout the remainder of her pregnancy and planned delivery for 37 weeks gestation. Her last dose of tinzaparin was administered 24 h prior to delivery. She delivered a healthy baby boy by caesarian section without any immediate complications.

Discussion

VTE in pregnancy is one of the leading causes of maternal mortality with close to one in 10 maternal deaths attributed to antepartum and postpartum PE.¹ The clinical presentation of PE is variable, and acute complications are similar to those seen in the nonpregnant population.² In pregnancy, therapeutic dose LMWH is the standard of care for the management of VTE (acute submassive/low-risk PE and deep vein thrombosis).³ When patients present with massive PE (Table 1), or if anticoagulation alone fails to improve the patient's condition, thrombolysis can be considered.⁴

Table 1. American Heart Association classification of pulmonary embolism⁴

Risk stratification of acute PE	Criteria (1 or more)
Massive	<ul style="list-style-type: none"> • Sustained hypotension (systolic BP <90 mm Hg for 15 min or requiring inotropic support) • Pulselessness • Sustained heart rate < 40 BPM with signs/symptoms of shock
Submassive	<ul style="list-style-type: none"> • Systolic BP > 90 mm Hg and RV dysfunction or myocardial necrosis defined by: <ul style="list-style-type: none"> • RV dilation (apical four-chamber RV diameter divided by LV diameter > 0.9) or RV systolic dysfunction on echocardiography • RV dilation (four-chamber RV diameter divided by LV diameter > 0.9) on CT • Elevation of BNP (> 90 pg/mL) or N-terminal pro-BNP (> 500 pg/mL) • ECG changes (new complete or incomplete right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion) • Elevation of troponin I (> 0.4 ng/mL) or troponin T (> 0.1 ng/mL)
Low-risk	<ul style="list-style-type: none"> • Normotensive, normal biomarkers, no RV dysfunction on imaging

PE pulmonary embolism; BP, blood pressure; BPM, beats per minute; RV, right ventricle; LV, left ventricle; BNP, B-type natriuretic peptide; CT, computed tomography; ECG, electrocardiogram.

Thrombolysis, either systemic with the use of fibrinolytic agents, or catheter-directed using pharmacologic and/or mechanical methods have been evaluated in nonpregnant patients, largely for massive PE.⁵ Whether to administer systemic thrombolysis for submassive PE remains controversial. A large, prospective, randomized control trial evaluating the impact of thrombolytic therapy on the long-term outcome of submassive PE showed that treatment with tenecteplase did not affect long-term mortality rates and did not significantly reduce functional limitations or RV dysfunction. Findings were limited by loss to follow-up, findings of late death not being centrally adjudicated, and the absence of clinical and echocardiographic evaluation on all survivors.⁶ Multiple prospective trials such as ULTIMA, PERFECT, and SEATTLEII have investigated the use of CDT for submassive PE. Results were promising, demonstrating improvements in surrogate outcomes such as reduction in pulmonary artery pressures. Drawing conclusions from these trials is challenging due to methodological flaws, including the use of surrogate outcomes, lack of long-term follow-up, and low statistical power.^{7–9} These studies excluded pregnant women, so evidence supporting CDT in this population is limited to case reports.^{10–16}

We identified seven published cases reporting CDT for PE in pregnancy with four being in submassive PE (Table 2).^{10–16} Five cases involved treatment with tPA and two with urokinase. The total dose administered and the duration of administration of the thrombolytic agent varied with each case. Furthermore, multiple cases involved concurrent additional therapies, particularly

mechanical thrombectomy, prior to the administration of thrombolytic agents. Of the case reports involving CDT, there was only one major bleed reported. There were no maternal deaths, and there was only one fetal loss, which the authors believed was not associated with the treatment.^{10–16}

Systemic thrombolysis in pregnancy carries the risks of maternal bleeding and fetal loss. In a recent review of pregnant patients treated with systemic thrombolysis, there was a 12.5% risk of major maternal bleeding and a 8.3% risk of fetal demise.¹⁷ The risk of bleeding with CDT is considered to be lower than with systemic thrombolysis because a lower dose of tPA is administered. With systemic thrombolysis, a typical dose of tPA to treat PE is 100 mg compared to CDT, where standard infusion rates of 1–2 mg/h result in a cumulative dose of approximately 15–30 mg.^{18,19} Although radiation exposure is an additional concern in pregnant patients, treatment totals were estimated to be approximately 118.8 mGy, which is equivalent to approximately — six to seven CT scans of the thorax. The dose of radiation to the fetus is estimated to be <1.4 mGy (approximated by 0.2 mGy dose per CT chest), which is significantly lower than the limit of 50 mGy, which, in turn, is associated with an increased risk of fetal loss and abnormalities.²⁰

We present a case of successful management of submassive PE in the first trimester of pregnancy with CDT. The optimal treatment of submassive PE is controversial. Current treatment guidelines recommend anticoagulation alone as the initial mode of treatment. In our case, the persistence of hypoxia and

Table 2. Summary of case reports of catheter-directed thrombolysis in pregnant women with submassive PE

Author	PE classification	Weeks' gestation	Treatment	Maternal outcome	Fetal outcome	Note
Krishnamurthy et al. (1999)	Submassive [†]	38 2/7	Initial treatment with 8,000 mg of IV UHF + 1000 mg/h infusion. 2,200 units/kg UK bolus + infusion of 2,200 units/kg/h for 24 h. IV UFH at 500 units/h and continued for 10 days with aPTT target 60–80 s. Heparin 15,000 U SC BID.	No major bleeding V/Q normal 6 weeks post CDT.	Delivered at 38 2/7 weeks following elective induction of labor.	Large azygos vein in place of IVC. Previous oral contraceptive pill provoked DVT. Family history of mesenteric artery thrombosis. Superficial vein thrombosis in early pregnancy.
Sofocleous et al. (2001)	Submassive	15	Initial heparin infusion. Balloon embolectomy and mechanical thrombectomy followed. CDT of 10 mg r-tPA to right pulmonary artery + 12 h at 2 mg/h.	Hemoptysis post initial heparin infusion. No major bleeding with tPA. Embolus absent on follow-up CT.	Fetal demise 24 h post tPA.	

Pick (2015)	Submassive	33	One dose of LMWH (dose not stated). 6 mg bolus of tPA in each infusion catheter plus continuous infusion at 0.5 mg/h following for 22 h. IV UFH infusion of 2300 units/h was maintained throughout the procedure. IVC filter post CDT for prevention prior to delivery. Therapeutic enoxaparin during hospitalization and on discharge. Subsequent CDT of DVT.	Complete resolution on pulmonary arteriography 22 h after treatment with normal perfusion bilaterally. Preeclampsia with severe features post-op day 11.	Medically induced labor at approximately 35 weeks	Concurrent right femoral DVT. Thrombophilia testing demonstrated Protein S deficiency and homozygous methylenetetrahydrofolate reductase C677T mutation was discovered after discharge.
O'Keeffe et al. (2008)	Submassive	38	Thrombus fragmentation with deferred catheter-directed lysis 3 days postpartum. Initial 50 mg tPA over 3 h into left and right lung, followed by 1 mg/h into left pulmonary artery and UFH at 500 U/h for 24 h. LMWH 6 h postpartum.	Episiotomy hematoma requiring surgical evacuation following UFH and continuous tPA. Complete resolution of emboli 24 h post tPA.	Spontaneous vaginal delivery.	Superficial phlebitis at 32 weeks treated with acetaminophen. Left common femoral vein DVT at presentation. 6 weeks post-partum discovered to have tubulocystic and papillary clear cell ovarian cancer.
Garbarino et al. (2017)	Massive	33	Initial treatment with oral ASA and Heparin. 2 mg tPA were injected into each PA, then continuous t-PA infusion of 1.2 mg/h for 17 h. Heparin infusion at a rate of 500 units/h was continued during this time. Enoxaparin SC on discharge.	No major bleeding described, improvement in cardiac function post treatment.	Normal intrauterine pregnancy at 33 weeks' gestation at time of discharge.	
Bechtel (2005)	Massive	30	IV Heparin infusion + IVC filter initially. 12 mg tPA bolus. 0.7 mg/h tPA infused into distal right pulmonary artery for 5 h. Peripheral IV heparin was restarted after the tPA infusion discontinued.		Uncomplicated delivery at 38 weeks.	Concurrent large femeropopliteal and peroneal vein DVT.

Weinberg et al. (2011)	Massive	31	Placed on ECMO after delivery. 30,000 IU UK combined with local suction embolectomy. Continuous 100,000 IU/h infusion for 24 h following. IVC filter placed temporarily and removed when INR therapeutic was initiated. Long-term Warfarin therapy.	Postpartum bleeding of 1000 cc. Right ventricular size and function and pulmonary artery pressures normalized 8 months post discharge.	Premature delivery at 31 weeks with thriving child on follow-up.	Postpartum pulmonary embolism during previous pregnancy treated with 6 months of warfarin. Enoxaparin 40 mg SC Daily prophylaxis starting second trimester of current pregnancy. Concurrent lower extremity DVT on presentation.
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IV intravenous; UK, Urokinase; UFH, unfractionated heparin; aPTT, activated partial thromboplastin time; V/Q, ventilation perfusion; CDT, catheter-directed thrombolysis; IVC, inferior vena cava; DVT, deep vein thrombosis; tPA, tissue plasminogen activator; CT, computed tomography; LMWH, low molecular weight heparin; SC, subcutaneous; IV, intravenous; IU, international units.

*Authors classify pulmonary embolism as massive, but based on American Heart Association guidelines, we reclassified it as submassive PE.

chest pain despite therapeutic dose anticoagulation, alongside significant RV dysfunction and elevated troponin levels prompted the consideration of thrombolysis. The reduced systemic dose of fibrinolytic drugs, minimal radiation exposure, and local procedural expertise made CDT an attractive option over systemic thrombolysis. CDT was performed successfully with no adverse effects to the mother or the fetus.

Conclusions

There is minimal data comparing systemic thrombolysis with CDT for the treatment of submassive PE in pregnancy. The literature published to date supports that CDT is safe in pregnancy but is limited to case reports. The optimal interventional technique is unknown. However, there is a biologic rationale to limiting systemic exposure to fibrinolytic agents in pregnancy. Our case adds to the extremely limited body of literature on the use of CDT in pregnancy and demonstrates that CDT in an appropriately selected patient can lead to a favorable clinical outcome for both mother and fetus.

Conflicts of Interest

This project did not receive any specific funding. Michael Radford and Michael Connolly do not have any commercial disclosures. Siraj Mithoowani received honoraria from Leo Pharma. Wendy Lim has received consulting fees from Pfizer Canada and Leo Pharma, and received honoraria for continuing her medical education from Alexion Pharmaceuticals, BMS-Pfizer Alliance, Fresenius, Leo Pharma, Novartis, Pfizer Canada, Pharmacosmos, and Portola Pharmaceuticals.

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