Thrombolytic Therapy for Acute Life-Threatening Pulmonary Thromboembolism in a Pregnant Woman

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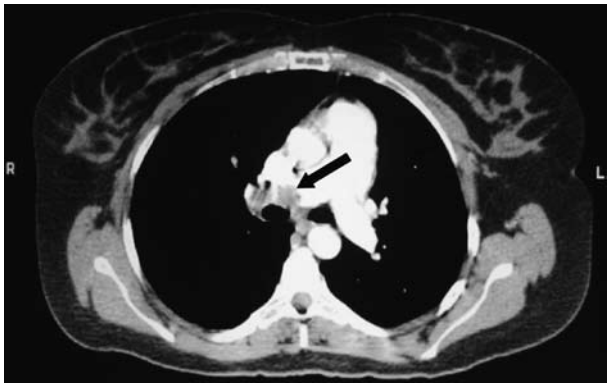
Pregnancy is a procoagulant state that minimizes intrapartum blood loss but also increases the rate of thromboembolic events. In the United States in 2000–2001, the overall risk of venous thromboembolism was 1.72 per 1000 deliveries and the risk of mortality was 1.1 per 100,000 deliveries, with a death rate of 2.4% among cases of pulmonary thrombembolism [1]. Massive PTE is one of the commonest causes of maternal/pregnancy-related death in the western world. In contrast to the unequivocal use of systemic thrombolytic therapy in massive PTE in the general population, in pregnancy such therapy was rarely reported, particularly in PTE. Moreover, recent clinical guidelines for anticoagulant and antithrombotic therapy do not address the issue of thrombolysis during pregnancy [2]. The present report describes the evolution of severe PTE in early pregnancy and discusses its complicated management decisions, with special attention to systemic thrombolytic therapy using recombinant human tissue plasminogen activator.

Patient Description

A 39 year old woman at 11 weeks gestation of her sixth pregnancy was admitted to our hospital because of severe dyspnea that started the day before. Her past medical history was unremarkable and her family history was negative for coagulopathy. On admission, her heart rate was 106/min, respiratory rate was 24/minutes, oxygen saturation on room air 89%, temperature 36°C, and systemic blood pressure 132/84 mmHg. Auscultation revealed reduced vesicular breathing over the right lower lobe. The patient was obese (body mass index 33). Laboratory findings showed: arterial blood gas while breathing room air pH 7.503, pO_2 56 mmHg, pCO_2 23 mmHg, base excess -4.4, and bicarbonate 18.2. Oxygen saturation on 2 L/m O_2 nasal prongs was 96%. A chest film showed hyperlucency of the right upper lobe. Electrocardiogram showed sinus tachycardia, S1, Q3, T3 pattern, and T wave inversion in leads V1-V3. Pulmonary thromboembolism was suspected. A ventilation-perfusion scan resulted in high probability for PTE. D-dimers were elevated to 3900 ng/ml. Troponin was normal. Doppler echocardiography showed normal left ventricle and dilated hypokinetic right ventricle. Estimated systolic pulmonary artery pressure was 59 mmHg.



Chest CT-angiography showing an obstructing embolus in the right main pulmonary artery

A diagnosis of sub-massive PTE was reached and unfractionated heparin was initiated intravenously at a mean daily dosage of 34,000 units. Mean activated partial thromboplastin time was 46 seconds. The patient remained stable until the fifth day when she suddenly experienced increasing shortness of breath and abdominal pain. Oxygen saturation dropped to 90% on 5 L/m O_2 nasal prongs and blood pressure fell to 90/60 mmHg. Recurrent PTE with development of massive PTE was suspected. Thrombolytic therapy with intravenous systemic rhTPA (100 mg/2 hr, Actylase®, Boehringer Ingelheim GmbH, Germany) was immediately instituted with a subsequent improvement in O_2 saturation. A compression ultrasound-Doppler of the lower extremities was performed on the seventh day due to leg pain, and a deep vein thrombosis of the left popliteal and saphenous veins was demonstrated. Obstetric consultation resulted in a clear recommendation to terminate the pregnancy. A chest angio-computed tomography scan done on the 12th day, before the abortive procedure, revealed multiple filling defects in the right upper and lower branches up to the right main pulmonary artery [Figure] and similar defects in the left lower lobe artery. Repeated Doppler echocardiography on the 14th day revealed normal heart chambers and estimated systolic pulmonary artery pressure of 38 mmHg. In view of a lower limb deep vein thrombosis an inferior vena cava retrievable filter was inserted on the 16th day, a day before the abortion. On the 17th day, aspiration curettage of the uterus was per-

PTE = pulmonary thromboembolism
rhTPA = recombinant human tissue prothrombin activator

formed without complications. Enoxaparin was instituted 12 hours later. Six days after IVC filter insertion a repeated compression ultrasound of the legs due to recurrent pain and swelling revealed an extension of the former thrombus to the common femoral vein. Ten days after IVC retrievable filter insertion, venography of the inferior vena cava revealed maldeviation of the filter's hook and intrafilter filling defects suspected as thrombi. The filter was left in place and warfarin was added to enoxaparin. Investigation for thrombophilia, partially limited by heparin treatment, was negative. The patient was discharged from the hospital on the 28th day on warfarin.

Comment

We describe a woman at 11 weeks gestation of her sixth pregnancy who presented with sub-massive PTE that soon deteriorated into a life-threatening massive PTE. The mainstay of treatment for massive PTE in non-pregnant individuals, unless there are contraindications, is urgent thrombolysis. This can be achieved preferentially by injection of a thrombolytic agent like rhTPA, systemically via a peripheral vein, or locally via a pulmonary artery catheter [2]. Surprisingly, although pregnancy is considered a procoagulant state and is an important risk factor for pulmonary thromboembolism, being the most common cause of maternal death in certain countries the issue of thrombolysis during pregnancy is not discussed in recent clinical guidelines. The guidelines [2] issued by the seventh American College of Chest Physicians conference on antithrombotic and thrombolytic therapy 2004 ignore this issue, probably due to the scarcity of published data. This will probably remain the case since randomized placebo controlled studies in this field are unlikely to be performed.

Is rhTPA use in pregnancy contraindicated? According to the U.S. Food and Drug Administration's use-in-pregnancy ratings for drugs, rhTPA is rated "C." Studies have demonstrated that placental transfer of rhTPA (molecular weight 72,000 kD) is too low to cause fibrinolytic effects on the fetus. Permanent sequelae have not been observed in children born after maternal thrombolytic therapy or in fetuses aborted for reasons unrelated to thrombolytic therapy [3]. Some reports documented complications such as maternal hemorrhage, preterm delivery, fetal loss, spontaneous abortion, minor vaginal bleeding, massive sub-chorionic hematomas, abortion placenta, uterine bleeding requiring emergency cesarean section, and postpartum hemorrhage that required transfusion. However, the complication rate of thrombolytic treatment does not seem higher than in the non-pregnant population, and complications occur mostly when thrombolytic therapy is administered intrapartum and if given concomitantly with heparin or oral anticoagulants [5].

Our patient first presented with a sub-massive PTE. Whether to treat patients (non-pregnant) suffering from sub-massive PTE with thrombolytic agents or with anticoagulation alone is a subject of continuing debate. The findings of a recent study [4] support early thrombolytic therapy in sub-massive PE in the general population. We could not find reports of thrombolytic therapy in sub-massive PTE during pregnancy. Whether a pregnancy should be terminated in the face of massive/sub-massive pulmonary thromboembolism in order to reduce maternal risk is not discussed in the literature either. It seems that each case needs to be approached individually. The mortality rate among pregnant women with pulmonary thromboembolism is 2.4% [1]. In the case of our patient described here, gestation age was only 11 weeks, in contrast with late pregnancy in most other case reports, and we therefore believed it essential to terminate the prolonged hypercoagulable state awaiting her. Obesity and age over 35 were two additional risk factors for thrombosis during pregnancy in our patient [1]. Our cautious approach was reinforced by the persistence of pulmonary thrombi in the angio-CT and the leg DVT a week after thrombolytic therapy was given, by the enlarging DVT, and finally by the imaging of new thromboemboli in the IVC filter despite continuous anticoagulation.

In summary, pregnancy and the postpartum period are hypercoagulable states of high risk for thromboembolism, especially PTE. We believe that the experience gained and described in the literature so far advocates rhTPA thrombolytic therapy in severe cases of pulmonary thromboembolism. The risk of untreated severe embolism to the mother and fetus is higher than the risk of rhTPA therapy. RhTPA should certainly be given for massive PTE, and in selected cases of sub-massive PTE. We also believe that in cases of life-threatening pulmonary thromboembolism termination of early pregnancy should also be considered in order to protect the mother. We encourage physicians to publish their experience with similar thromboembolic events that require thrombolytic therapy, and clinical guidelines committees to review the published experience, even if uncontrolled, so that recommendations will be incorporated in future editions of clinical guidelines for the management of severe thromboembolic complications during pregnancy.

IVC = inferior vena cava

DVT = deep vein thrombosis

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