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Review Article

Treatment options in massive pulmonary embolism during pregnancy; A case-report and review of literature

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ABSTRACT

Systemic thrombolysis with recombinant tissue plasminogen activator (rt-PA), streptokinase or urokinase is considered as high-risk treatment in pregnancy. However, several reports have described the successful use of systemic thrombolysis in pregnant patients with massive pulmonary embolism and haemodynamic instability. *Case:* We describe a 34-year old, pregnant female, who presented at 25 weeks of gestation with an acute collapse with reduced consciousness and shortness of breath caused by massive pulmonary embolism. Because of significant haemodynamic instability, increased right ventricular pressure and no improvement after intravenous heparin, thrombolytic therapy was administered. The response to thrombolytic therapy was excellent. No severe haemorrhagic complications were observed. Anticoagulant therapy with LMWH was continued until delivery. A healthy child was born at term. *Review:* In English literature, 13 patients received thrombolysis during pregnancy because of pulmonary embolism. No maternal deaths, four non-fatal maternal major bleeding complications, 30.8%;95%CI(9.1-61.4), two fetal deaths, 15.4%;95%CI(1.9-45.5), and five preterm deliveries, 38.5%;95%CI(13.9-68.4), were observed. Surgical embolectomy and catheter embolectomy or catheter thrombolysis has only been performed in 12 patients. *Conclusion:* The number of reports on thrombolytic therapy, surgical embolectomy and catheter embolectomy or thrombolysis for massive pulmonary embolism during pregnancy are limited. We suggest an international registry for pregnant patients undergoing thrombolysis or embolectomy to gain more information about these treatment options. Nevertheless, complication rates of thrombolytic therapy are acceptable in the light of the underlying disease, and in the meantime, current data do not justify withholding pregnant women from thrombolytic therapy in case of life-threatening PE.

Contents

Introduction

The incidence of venous thromboembolic events (VTE) is the second cause of maternal death in the Netherlands and the most important cause of maternal death in the UK [1,2]. The exact incidence of VTE during pregnancy and puerperium is unknown, but estimations vary from 0.5-3.0 per 1000 pregnant women [3,4] and is up to ten times more common in

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pregnant women as compared to non-pregnant women [5]. Eighteen percent (35/193) of direct maternal deaths in pregnancy in the Netherlands between 1993 and 2000 were related to VTE [1]. VTE can occur at any stage of pregnancy but there is a higher risk in the puerperium. During pregnancy there are changes in the maternal haemostatic system which tend to prevent haemorrhage, but predispose to thrombosis [6]. Thrombosis is also aggravated by inherited and acquired maternal thrombophilias [6].

Because of the relatively high incidence and mortality rate of VTE in pregnancy, effective primary prevention and adequate management of thromboembolism in pregnancy are important. Treatment of VTE in pregnancy constitutes a challenge in daily clinical practise, because of possible haemorrhagic and teratogenic complications for mother and fetus. Low-molecular-weight heparin (LMWH) and intravenous unfractionated heparin (UFH) are used for prevention and treatment of VTE in pregnancy, with a preference for LMWH [7]. Treatment options for non-pregnant patients with severe, life-threatening pulmonary embolism, with haemodynamic compromise or failure of therapy with heparin include thrombolytic therapy, surgical embolectomy and catheter embolectomy or catheter thrombolysis. These options are considered as high-risk treatment in pregnancy and possibly harmful for mother and fetus. We describe a pregnant patient with massive pulmonary embolism who successfully received thrombolytic therapy and review the available literature on the outcome of aggressive therapy, i.e. thrombolytic therapy and embolectomy, in case of pulmonary embolism during pregnancy.

Case report

A 34-year-old female, gravida 1, presented at 25 weeks gestation with an acute collapse, reduced consciousness during five minutes and shortness of breath. At physical examination the patient had dyspnoea with a, respiratory rate of 30 per minute and hypoxaemia (O_2 saturation 80% on room air), hypotension (blood pressure of 80/30mmHb) and a sinus tachycardia (115 bpm). Heart sounds revealed an ejection murmur. Electrocardiography demonstrated sinus tachycardia with T wave inversion in lead III and V1, V2 and V3. The condition of the fetus, assessed by ultrasound, was normal. The clinical presentation was highly suggestive of pulmonary embolism. Ventilation-perfusion scan showed massive pulmonary embolism with absence of perfusion of almost the entire right lung and a part of the left upper and lower lung. A trans-thoracic echocardiosonography demonstrated a severely enlarged right ventricle and atrium with increased right pressure and moderate tricuspid regurgitation. Therapy was initiated with intravenous heparin, but because of massive pulmonary embolism with significant haemodynamic compromise, increased right ventricular pressure and no improvement after administering heparin, the decision was made to start thrombolytic therapy using streptokinase. The patient received streptokinase as a bolus of 250.000 units followed by a continuous infusion of 100.000 units per hour during 24 hours followed by a weight-adjusted dose of LMWH. The response to thrombolytic therapy was remarkable: the tachycardia and dyspnoea resolved completely and blood pressure and heart rate normalised. Ultrasound revealed no signs of placental or fetal bleeding. The patient developed large subcutaneous haematomas, on the site of the skin injuries due to the collapse, which required two units of red blood cell transfusion. After discharge the pregnancy developed uneventful. LMWH was continued until delivery. A healthy child was born at 41 weeks of gestation by an uncomplicated vaginal delivery with minimal blood loss. A successive lung perfusion scan showed complete resolution of the pulmonary emboli. Acenocoumarol treatment was initiated after delivery and continued for a period of 6 weeks. The total period of anticoagulation therapy was 22 weeks.

Thrombolytic therapy

In non-pregnant patients, thrombolytic therapy is recommended in case of massive pulmonary embolism and haemodynamic compromise or cardiogenic shock [8,9]. Several randomised trials have proven that thrombolytic therapy cause more rapid dissolution of the emboli in the first 24 hours and improves haemodynamics earlier as compared to heparin, but without evidence of survival advantage on the long term [8,10,11]. Mortality rates from massive pulmonary embolism in non-pregnant patients are exceptionally high with rates ranging up to 46.3% in patients with a systolic pressure <90 mmHg [15]. Major bleeding complications due to thrombolysis in non-pregnant patients vary from 0.8% to 8.4% [13,16]. The most commonly used thrombolytic agents are streptokinase, urokinase and recombinant tissue plasminogen activator (rt-PA). The safest and most effective treatment is yet unknown, but there seems to be a slight preference for rt-PA because of less haemorrhagic complications and a lower mortality rate [12,13]. Rt-PA is not allergenic and can be administered over a shorter time scale. Rt-PA is a large polypeptide that does not cross the placenta [17,29]. Streptokinase is also a large molecule derived from group C streptococci, which does not cross the placenta in amounts significant enough to induce fetal coagulopathy [14]. Urokinase is a small molecule purified from human urine; it does cross the placenta [17]. It is currently not known whether urokinase induces fetal coagulopathy, but this can not be excluded from its pharmacological profile.

We conducted a PubMed (National Library of Medicine, Bethesda, MD) search with the subject headings “thrombolytic therapy”, “thrombolysis”, “pregnancy” and “pulmonary embolism” to identify reports of pregnant women who received treatment with thrombolytic therapy during pregnancy because of pulmonary embolism. Reports with postpartum pulmonary embolism and reports in which therapy was administered after delivery by emergency caesarean section because of pulmonary embolism were excluded. We limited our search to English literature. Data on the type and total dose of thrombolytic agent, gestational week, outcome of mother and child, preterm delivery and bleeding complications were extracted. Twenty-two cases were found till December 2008, two were excluded because of postpartum pulmonary embolism, two were excluded because of initiation of thrombolytic therapy after caesarean section and six cases were excluded because of non-English literature. In summary, we only found 13 cases (including our own case) of patients who received thrombolytic therapy for pulmonary embolism during pregnancy, 6 cases with rt-PA, 5 cases with streptokinase and 2 cases with urokinase (Table 1) [17–28]. Median gestational time was 26 weeks, with a range from 12 to 35 weeks. There have been no maternal deaths, four non-fatal maternal major bleeding complications, 30.8%; 95% CI (9.1-61.4), two fetal deaths, 15.4%; 95% CI (1.9-45.5) and five preterm deliveries, 38.5%; 95% CI (13.9-68.4), all just after initiation of thrombolytic therapy (Table 1). According to the authors, the fetal deaths and preterm deliveries were supposed to be primarily related to the sequelae of pulmonary embolism (Table 1).

Three reviews on the use of thrombolysis during pregnancy for different indications, including pulmonary embolism, deep venous thrombosis, thrombosis of cardiac valvular prosthesis, myocardial infarction and stroke, have been published [17,29,30]. Ahearn *et al* published a review with 172 cases (164 treated with streptokinase, 3 urokinase, 5 rt-PA), including 10 cases of pulmonary embolism (these cases are included in Table 1 with exception of the cases from non-English literature). They reported 5 non-fatal maternal bleeding complications (2.9%) and 3 fetal deaths (1.7%). No maternal deaths from thrombolytic therapy have been reported. Turrentine *et al* reviewed 172 cases (165 streptokinase, 3 urokinase, 4 rt-PA) with 8.1% maternal bleeding complications, 5.8% pregnancy losses and 5.8% preterm deliveries. They found two maternal deaths (1.2%), which could not be related to thrombolytic therapy, according to the authors. Most cases (n = 155) were described by German investigators, who treated pregnant women with streptokinase because of deep venous thrombosis [14,31,32].

We compared complication rates from patients treated with thrombolysis because of other indications than PE in pregnancy extracted