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Thrombolytic therapy in pregnancy

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Abstract. **Pregnancy due to its physiological changes is a procoagulant state. The rate of cardiac valve prosthesis thrombosis, deep venous thrombosis and pulmonary embolism are all increased. Thrombolytic therapy with tissue plasminogen activator (rt-PA) is an approved therapy for ischemic stroke, myocardial infarction, pulmonary embolism and thrombosis of cardiac valve prosthesis. However, there are no data from controlled randomized trials in pregnant patients. Thrombolytic therapy has been rarely used in pregnancy with only 28 cases of rt-PA thrombolysis reported in the literature so far. Indications for rt-PA thrombolysis were stroke ($n = 10$), thrombosis of cardiac valve prosthesis ($n = 7$), pulmonary embolism ($n = 7$), deep venous thrombosis ($n = 3$), and myocardial infarction ($n = 1$). Remarkably, all thrombosis of cardiac valve prostheses occurred after switching from warfarin to heparin in order to prevent teratogenicity and fetal loss. Two patients died (7%) and three suffered from complications that were managed conservatively (11%). In another three patients thrombolysis was not successful. Thrombolysis complication rates were similar compared to non-pregnant patients for the above mentioned indications. Six out of the 26 fetus from surviving mothers died (23%), three of them after induced abortion for maternal reasons (12%). A likely causal relation to the prior thrombolysis could only be established in two fetal fatalities (8%). None of the live born children suffered a permanent deficit.**

Considering that rt-PA does not cross the placenta and taking into account that the complication rates do not exceed those of large randomised controlled trials thrombolytic therapy should not be withheld in pregnant patients in case of life-threatening or potentially debilitating thrombembolic disease.

Key Words. **thrombolytic therapy, rt-PA, pregnancy, stroke, pulmonary embolism, cardiac valve thrombosis, myocardial infarction.**

Introduction

During pregnancy procoagulatory mechanism dominate over prolytic ones leading to an increased rate of deep venous thrombosis, pulmonary embolism and thrombosis of cardiac valvular prosthesis, less often ischemic stroke and myocardial infarction. For ischemic stroke thrombolytic therapy is the only one approved, for myocardial infarction, pulmonary embolism, and thrombosed cardiac valve prosthesis it is one of few approved recanalizing therapies. Today recombinant tissue plasminogen activator (rt-PA, Alteplase) or one of its newer derivates are preferred over streptokinase and is recommended in the guidelines due to its high fibrin specificity, absence of antigenicity, and short serum half-life.

Thrombolytic therapy is indicated in case of acute ST-elevation myocardial infarction (STEMI) within the first six hours if percutaneous coronary intervention is not feasible or available [1], in case of pulmonary embolism with positive shock index and hemodynamic instability [2], and ischemic stroke within the first three to six hours if cerebral hemorrhage is excluded by CT or MRI imaging. There are no evidence-based guidelines for thrombosed cardiac valve prosthesis, since this complication is rare. Based on case series it was recommended to use thrombolysis in acute or subacute thrombosis of the right ventricle and in patients with unstable hemodynamics [3].

According to the pharmaceutical prescription guidelines pregnancy and the first post partum week are no contraindications for the treatment with alteplase. However a thorough risk-benefit evaluation is recommended [4]. Pregnant patients were excluded from the phase-II and phase III-trials of alteplase. Most probably there won't be randomized controlled trials of thrombolytic therapy during pregnancy in the near future. Hence data from case reports and case series are yet the best level of evidence we have. In the clinical routine physicians refrain from thrombolytic therapy during pregnancy since they fear to harm the mother or fetus. Streptokinase and urokinase are only rarely used anymore in most developed countries. Therefore these substances are not included in this paper.

Incidence and prevalence of thrombembolic diseases during pregnancy

Stroke is a rare event during pregnancy. A population based study showed that the incidence of ischemic brain infarction in pregnant women (0.03/1000 pregnancies, relative risk (RR) 0.7) is less than in age matched controls. During the immediate postpartum period the incidence is increased (RR 2,5) [5]. In a retrospective case-control-study of 50.711 deliveries eight ischemic brain infarctions and one cerebral sinus thrombosis were identified. Most events occurred

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during the first ($n = 3$) and the third trimester ($n = 4$) [6].

Deep venous thrombosis and pulmonary emboli are four to six times more common during pregnancy. Incidence rates increase with pregnant patient age: 0.615/1000 (age below 35 years) and 1.216/1000 pregnancies (age beyond 35 years) for deep venous thromboses, 0.108/1000 and 0,405/1000 pregnancies for pulmonary embolism [7–8].

Thrombosis of cardiac valve prosthesis is rare. During pregnancy the incidence increases depending on the anticoagulation regime (9.2% with heparin, 3.9% with warfarin) [9].

The incidence of myocardial infarction is 1/10.000 pregnancies with a case fatality between 37 and 50%, which increases in age below 35 years, when the event is close to the time of delivery and in case of cesarean section [10].

Teratogenicity

Studies on rats and rabbits did not find any teratogenicity using doses of 10 mg/kg/day [11–12]. Studies on rats did not find disturbances of postnatal development in doses up to 3 mg/kg/day [13]. Due to its large molecular size (72000 kd) rt-PA does not cross the placenta.

Thrombolytic therapy with rt-PA during pregnancy

A Medline-research (search terms: "thrombolysis or thrombolytic therapy" and "pregnancy") and hand search identified 20 case reports in 19 patients and two published abstracts on seven patients (see table 1). Including an own case report (see figure 1 and 2) there are 28 reports on rt-PA thrombolysis during pregnancy up to now. The underlying diseases were stroke ($n = 10$, including one cerebral sinus thrombosis), thrombosis of cardiac valve prosthesis ($n = 7$), pulmonary embolism ($n = 7$), deep venous thrombosis ($n = 3$), and myocardial infarction ($n = 1$). Case reports with postpartum thrombolysis and usage of other thrombolytic drugs were not included.

Stroke and cerebral sinus thrombosis

There are three case reports on rt-PA application for stroke during pregnancy (systemic in two, and intraarterial application in one patient [14,15, own case]. Dosage was 0.9 mg/kg for one hour in case of systemic application, and 15 mg in case of intra-arterial application. Two of the three patients had a good outcome [14–15], the third patient suffered from permanent dense hemiparesis (own case report, see figure 1 and 2). All children were healthy, one child was delivered by cesarean section due to premature labor.

A published abstract reports on six women including two patients who had been treated with urokinase [16]. One patient, who was treated with intraarterial thrombolysis deceased after malignant ischemic brain infarction due to arterial dissection. Two patients suffered from intraabdominal and intragluteal hematoma, respectively, which could be managed conservatively. Two children had an uneventful delivery. In three patients an abortion was induced due to maternal reasons. No further information on the exact reasons for the abortions and the allocation of the patients to the administered thrombolytic drug were given.

One patient with cerebral sinus thrombosis suffered a delayed deterioration after the first treatment with 48 mg rt-PA and underwent a second successful thrombolytic treatment. The child had an uneventful delivery [17].

Thrombosis of cardiac valve prosthesis

Thrombosis of artificial cardiac valves can cause severe hemodynamic compromise. So far seven pregnant patients with thrombolytic therapy due to thrombosed cardiac valve prosthesis have been published (aortic valve $n = 1$, mitral valve $n = 5$, tricuspid valve $n = 1$). In the case of the tricuspid valve, which has been published twice, vaginal bleeding, re-thrombosis and unsuccessful second thrombolysis was reported. Due to imminent hemodynamic failure an abortion and hysterectomy with a subsequent surgical valve replacement was performed [18–19]. The patient with thrombosed aortic valve prosthesis showed a quick recovery after thrombolysis, the child was delivered healthy by cesarean section in the eighth gestational month [20]. One out of five patients with thrombosed mitral valve prosthesis died due to cardiogenic shock [21]. Another mitral valve patient showed an incomplete response but benefited to such an extent that the pregnancy could be carried to term [22]. The other three patients had a favorable outcome [21,23,24]. It is remarkable that in all eight cases oral anticoagulation had been replaced by subcutaneous high-dose heparin (unfractionated heparin in five, low molecular weight heparin in two) shortly before the valve thrombosis occurred.

Pulmonary embolism

Seven pregnant patients with severe pulmonary embolism had a good outcome after thrombolytic therapy. Five of seven children were delivered healthy at term [25–29]. One child died due to spontaneous abortion 24 hours after thrombolytic therapy [30]. According to the opinion of the reporting authors this complication was due to severe hemodynamic failure during the pulmonary artery occlusion rather than due to the adverse reactions of rt-PA. Another

Table 1. *Case reports on thrombolytic therapy for pulmonary embolism, deep venous thrombosis, thrombosed cardiac valvular prosthesis, myocardial infarction, and stroke during pregnancy.*

Author	Year	N	Indications	Dosage, mode of application	Gestational week	Outcome mother	Outcome child	Complications/ peculiarities
Ahearn, GS	2002	1	PE	100 mg i.v.	12.	good	good	none
Baudo, F	1990	1	PE	100 mg i.v.	35.	good	death after 14 d	congenital AT-III-deficiency
Floßdorf, Th	1990	1	PE	43 mg i.v.	31.	good	good	Premature delivery
Patel, R	2003	1	PE	100 mg	20.	good	good	Anti-thrombin-deficiency
Seifried, E	1991	1	PE	60 mg i.v.	11.	good	good	none
Sofocleous, C	2001	1	PE	34 mg for 12 h i.a.	15.	good	Spontaneous abortion	Spontaneous abortion 24 hours after thrombolysis
Yap, L	2002	1	PE	100 mg i.v.	30.	good	good	none
De Stefano, V (Abstract)	1991	1	DVT	50 mg i.v. twice	26.	good	good	Cesarean section in 33.gestational week
Grand, A	1996	1	DVT	80 mg i.v.for 3h	31.	Reperfusion of femoral artery, Occlusion of ext. iliac artery	good	none
Behrendt, P	2001	1	DVT	50 mg i.v.for 2 h	17.	good	good	none
Azzano, O/Di Roio, C	1994/1995	1	Tricuspidal VP	40 mg i.v. for 8 h	17.	Thrombolysis not successful, Surgical valve replacement	Abruption due to maternal reason	Severe abdominal hemorrhage, abruption and hysterectomy, surgical valve replacement
Fleyfel, M	1990	1	Mitral VP	50 mg i.v.	28.	good	good	Previous surgical repair of MVP in 20. gestational week
Nanas, J	2001	1	Mitral VP	100 mg i.v.	25.	good	good	none
Nassar, AH	2003	1	Mitral VP	Streptokinase, rt-PA 100 mg i.v.	26	No success good	good	sequential application of 2 thrombolytics
Rinaldi, J	1999	1	Aortic VP	50 mg i.v.	15.	good	good	8th month Cesarean section
Sahnoun-Trabesi, I	2004	2	Mitral VP	Not specified	12.	death		Cardiogenic shock
			Mitral VP	Not specified	8.	good	good	
Schumacher, B	1996	1	Myocardial infarction	100 mg i.v.	21.	good	good	Cesarean section due to premature labour
Dapprich, M	2002	1	Stroke	0,9 mg/kg i.v.	12.	good	good	Minor hemorrhagic imbition of infarct area
Own observation	2004	1	Stroke	60 mg i.v.	23.	Basal ganglia infarction	good	Anti-phospholipid antibody syndrome
Elford, K	2002	1	Stroke	15,5 mg i.a.	1.	Recanalization, minor hemorrhage	good	Ovarian hyperstimulation syndrome after IVF
Murugappan, A (Abstract)	2000	4 + 2 UK	Stroke	Not specified	4.–37. (Mean 15)	1 fatality, 1 intrabdominal hematoma, 1 intramuscular hematoma	2 normal deliveries, 1 spontaneous abortion, 2 abruptions due to maternal reasons	1 child affected by thrombolysis, allocation of patients to drug not feasible
Weatherby, SJM	2003	1	Cerebral sinuous thrombosis	48 mg i.a. 48 mg i.a.	9.	Re-occlusion good	good	Re-occlusion and second thrombolysis

PE: pulmonary embolism. DVT: deep venous thrombosis. Mitral VP: thrombosed mitral valve prosthesis. Triscupid VP: thrombosed thicuspid valve prosthesis. Aortic VP: thrombosed aortic valve prosthesis. UK: Urokinase. i.a.: intraarterial. IVF: in vitro fertilization.

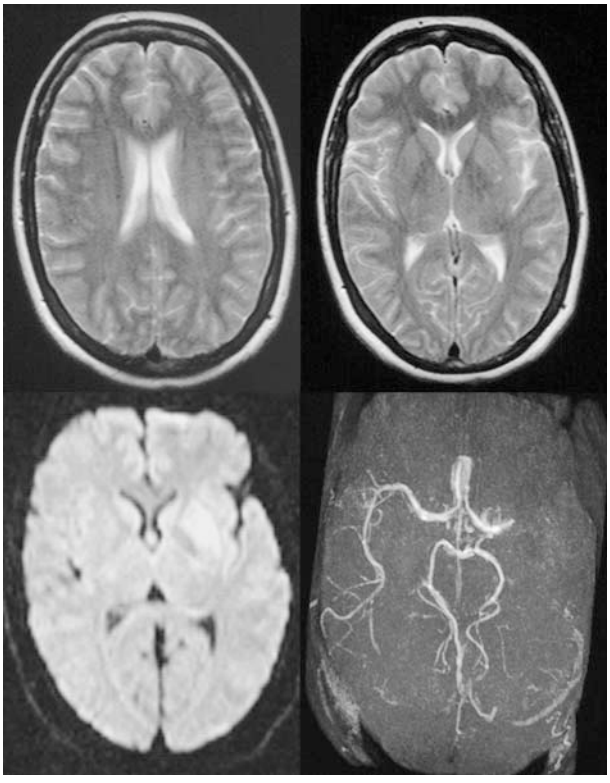

Fig. 1. *Magnet resonance imaging and magnet resonance angiography at the time of admission show normal FLAIR (left) and T2-imaging (right, upper row), hyperintense signal in diffusion imaging (left) and occlusion of the MCA left (right, lower row).*

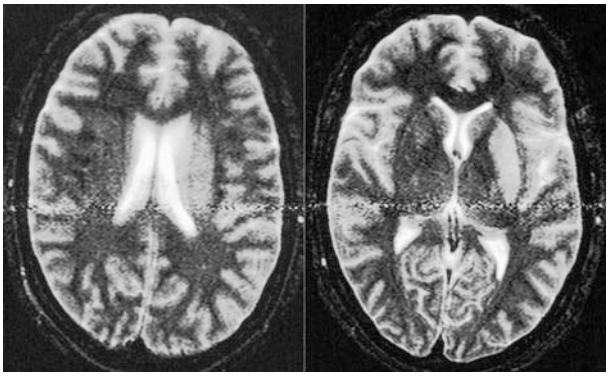

Fig. 2. *Magnet resonance imaging at the following day shows demarcation of a basal ganglia infarction after thrombolysis without hemorrhage. The MCA is partially re-occluded (not shown).*

child which was born in the 35th week died a fortnight later due to neonatal respiratory distress syndrome [31]. Autopsy revealed multiple intracerebral und subarachnoidal hemorrhages which were classified as sequelae of the respiratory distress syndrome.

Deep venous thrombosis

Three patients had a good clinical outcome and a complete or partial reopening of the occluded vessels. All three children were delivered healthy [32–34].

Discussion

Two out of 28 patients with thrombolysis of thrombembolic diseases during pregnancy died (7%). Three patients suffered from complications which could be managed successfully (11%). In three patients thrombolytic therapy was not successful (11%). The two fatalities were not directly related to the application of rt-PA; in one case the underlying disease and in the other case the mechanical manipulation with subsequent vascular lesions were the fatal factors. Six out of 25 children of the surviving patients died (24%), five directly following the thrombolytic therapy, one premature neonate died two weeks postpartum. Three out of the five prenatal fatalities were due to abortion for maternal reasons, no affection of the fetus had been reported. Taken together only in two cases a causal relationship of fetal death with rt-PA application is probable (8%).

Remarkably, in all cases of thrombosed cardiac valvular prosthesis oral anticoagulation had been replaced by subcutaneous high dosage heparin to avoid the known teratogenicity of about 6–7% and high abortion rate of 30–70% of cumarin derivates. Unfractionated and low molecular weight heparins do not cross the placental barrier und hence are not teratogenic nor do they cause hemorrhage in the fetus. Vice versa, thrombosis of valvular prosthesis are more often on heparin therapy (9.2% vs. 3.9%) than on warfarin [9].

Complication rates of thrombolytic therapy in pregnant patients are not higher than in the large randomized trials on stroke, myocardial infarction and pulmonary embolism [35–39]. The case fatality was 6.1 to 6.3% in the stroke studies [35,36], 6.3 to 9.3% in the myocardial infarction studies [38] and 6% in a study on pulmonary embolism [40]. Intracranial hemorrhage, which was not yet observed in pregnant patients, had an incidence rate of 10.8 to 19.8% in the stroke studies [35,36,39], 5% in a pulmonary embolisms study [37], and 0.7 and 0.9% in studies on myocardial infarction [38]. The rate of abortion and still birth (8%) after thrombolytic therapy is only slightly higher than in the general population [41,42]. Permanent sequelae have not been observed in the surviving children.

Due to scarce data it must not be concluded that pregnant patients and their unborn children are not at risk to be affected by thrombolysis. Since it is rather improbable that these patients will be included in randomized controlled trials in the near future, evidence can be derived only from case reports and small case series.

When a certain therapy is considered to be applied its complication rates have to be weighted against the risks and benefits of alternative procedures. In case

of stroke thrombolytic therapy is the only approved therapy to establish reperfusion. In case of myocardial infarction percutaneous angioplasty is the preferred treatment despite its x-ray exposure. Thrombolytic therapy of pulmonary embolism is applied in severe cases and is equally effective compared to surgical thrombectomy. In case of thrombosed cardiac valvular prosthesis surgery is the alternative to thrombolysis. According to expert opinion cardiac surgery using the cardiopulmonary bypass circuit exposes mother and child to a greater risk than thrombolytic therapy does [3].

In conclusion, currently available data are not sufficient to derive guidelines for rt-PA thrombolysis in pregnancy. However, we feel that it is not justified to withhold thrombolytic therapy from pregnant patients if effective alternatives are lacking. The moderate rate of maternal and fetal complications and the absence of teratogenicity and fetotoxicity make thrombolysis a valuable therapeutic option in some pregnant patient with stroke, thrombosed cardiac valvular prosthesis, acute myocardial infarction and pulmonary embolism if performed by an experienced physician.

Case report: Thrombolytic therapy of a 26 year old pregnant patient

The 26 year old patient in her 23rd gestational week noticed weakness of her right arm on awakening. She presented with dense hemiparesis of the right side in the emergency department. Speech was not affected (left handedness). Diffusion weighted MR imaging showed hyperintensity of the left basal ganglia and occlusion of the medial cerebral artery M1 segment (see figure 1). Thrombolytic therapy with alteplase 0.9 mg/kg of body weight for one hour was started. After two hours re-opening of the vessel was seen on transcranial ultrasound. Hemiparesis was considerably improved. On the following day the right arm paresis deteriorated with leg strength being improved. The MR imaging showed demarcation of an acute ischemic infarction in the basal ganglia and partial re-occlusion of the MCA (see figure 2). No hemorrhage was seen. Cardiotocogram and ultrasound did not show abnormality of the fetus. Further work-up revealed elevated IgG and IgM anti-cardiolipin antibodies (46 GPL-U/m, 8.1 GPL-U/ml, respectively). Anticoagulation with subcutaneous low molecular weight heparin was initiated. The patient was transferred to the rehabilitation unit on day 9. Premature vaginal delivery of a healthy boy occurred in the 32nd + 6 gestational weekwith a birth weight of 2100 grams, (length 43 cm, APGAR 3/7/8, NA-pH 7.00). The boy is reported healthy at one year follow-up.

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