Acute Revascularization Therapy in Pregnant Patients

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Abstract

Ischemic stroke is uncommon during pregnancy, but decision making for acute revascularization therapy including intravenous recombinant tissue plasminogen activator (rt-PA) is difficult. The use of rt-PA remains controversial, but a systematic review of 16 patients (mean age 31.7 years) showed good results for both maternal (77.8%) and fetal (56.3%) outcomes. Pregnancy alone is not a solid contraindication for acute revascularization therapy including rt-PA. An endovascular approach might be beneficial for reducing the hemorrhagic complication; however, the treatment strategy should be considered based on the available treatment facility. Close cooperation with obstetrics is essential for the successful management of saving the lives of both the mother and the fetus.

Key words: pregnancy, acute ischemic stroke, recombinant tissue type plasminogen activator, revascularization therapy

Introduction

In general, ischemic stroke is uncommon during pregnancy. However, the treatment decision after stroke is quite difficult, as the benefits of acute revascularization therapy are sometimes offset by the potential harm to the fetus. Here, we summarize previous reports on the incidence of stroke during pregnancy, and discuss the controversy regarding the use of acute revascularization therapy based on reported case series of stroke during pregnancy.

Incidence of Ischemic Stroke During Pregnancy

The reported incidence of stroke during pregnancy varies widely, due to differences in surveillance methods (Table 1). Recent large-scale population-based studies have estimated the incidence to be 4 to 11/100,000 pregnancies.23,41,47) Among 1,051,113 residents recruited in the Baltimore-Washington Cooperative Young Stroke Study,24) 17 cerebral infarctions occurred during 8,011,852 woman-weeks of exposure, whereas 175 cerebral infarctions occurred during 101,303,016 non-exposed woman-weeks. On the other hand, the RR increased to 5.4 (95% confidence interval 2.9–10.0) during the postpartum period (after live birth or stillbirth).

Arterial events occur in the first and third trimesters, whereas venous events frequently occur postpartum.21) Etiologic diagnosis is usually difficult to establish, but possibilities include cardiac emboli, coagulopathies, and carotid artery dissection.28) A summary of 102 patients (mean age 28.9 ± 1.6) from seven studies revealed that 37.3% of strokes were related to eclampsia, 25.5% to cardiac disease, 7.8% to coagulopathy, and 2.0% to atherothrombosis.47)

Treatment Strategy for Acute Ischemic Stroke in Pregnancy

Balancing the maternal benefit and risk of any given therapy as well as the potential fetal harm is key for developing a treatment strategy. The main purpose
Table 1 Frequency of ischemic stroke during pregnancy

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Method of survey</th>
<th>Period</th>
<th>Number of pregnancies</th>
<th>Number of ischemic strokes</th>
<th>Frequency of ischemic strokes /100,000 pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ros et al. (2001)*</td>
<td>retrospective, birth registry</td>
<td>1987–1995</td>
<td>1,003,489</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Jeng et al. (2004)*</td>
<td>retrospective, single hospital registry</td>
<td>1984–2002</td>
<td>49,796</td>
<td>16</td>
<td>32.1</td>
</tr>
<tr>
<td>Scott et al. (2012)*</td>
<td>retro-/prospective, population based study</td>
<td>2007–2010</td>
<td>NR</td>
<td>NR</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Cited from ref. 10). NR: not reported.

of revascularization therapy is to improve stroke symptoms and minimize residual deficits. Amongst the various strategies, thrombolytic therapy using intravenous recombinant tissue plasminogen activator (IV rt-PA) has been established as highly successful in acute stroke therapy.45) Although IV rt-PA increases the risk of bleeding and sometimes results in fatal outcomes,34) adequate use under the recommended guidelines minimizes the risks and potentiates effects of the therapy.1,3,14,18)

On the other hand, risk assessment for the fetus, including placental separation and uterine hemorrhage, is essential. Although alteplase does not transfer to the placenta because of its high molecular weight and is not reported to be teratogenic,26) as confirmed in animal studies,25,43) adequate use under the recommended guidelines minimizes the risks and potentiates effects of the therapy.1,3,14,18)

Endovascular therapy can reduce the dose or even be performed without thrombolytic agents.7) This is a major advantage of the catheter-based strategy, though x-ray exposure is inevitable.12,29,36) Among other antithrombotic agents used after endovascular therapy, heparin has no side effects for the fetus,15,19) Warfarin is a well-known contraindication for pregnant and breast-feeding women, because of its teratogenic (fetal warfarin syndrome) and hemorrhagic complications.4,30,38)

Description on Package Leaflet: Alteplase for Pregnant Women

The latest updated systematic review, including the Third International Stroke Trial,37) showed that IV rt-PA administered within 6 hours of stroke onset significantly increased the number of patients that could live independently (modified Rankin scale 0–2) at 3 months (46.3% vs. 42.1%).45) However, pregnancy is a solid contraindication of all clinical trials of IV rt-PA.18,34,40) Therefore, the major guidelines for IV rt-PA are silent on this issue.

In the Japanese package leaflet, the description of the use of alteplase during pregnancy is given as follows: Alteplase should be administered to pregnant or possibly pregnant women if the therapeutic benefit outweighs the risk. Animal studies (rabbit) have revealed embryo-fetal death under high dose administration. The fibrinolytic activity might cause early separation of the placenta.

The US Food and Drug Administration classified alteplase in Pregnancy category C, that is: Risk cannot be ruled out. Adequate, well-controlled human studies are lacking and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy; but the potential benefits may outweigh the potential risk. In Australia, alteplase is categorized as C: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. According to these official notifications, IV rt-PA using alteplase during pregnancy is not prohibited. The benefit (mainly for maternal curative effect) from the therapy and risk for both mother and fetus should be judged quickly, but systematically, and a firm decision made.

Case Reports of Acute Revascularization Therapy During Pregnancy

As of March 2013, 16 patients (mean age 31.7 ± 5.4 years, 8 in the 1st trimester, 4 in the 2nd, and
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Age (yrs)</th>
<th>Gestational week</th>
<th>Cause</th>
<th>Revascularization</th>
<th>Dose</th>
<th>Complication</th>
<th>Outcome</th>
<th>Delivery</th>
<th>Fetal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapprich and Boessenecker (2002)</td>
<td>31</td>
<td>12</td>
<td>PS deficiency</td>
<td>IV rt-PA</td>
<td>0.9 mg/kg</td>
<td>H/I</td>
<td>good</td>
<td>normal delivery</td>
<td>good</td>
</tr>
<tr>
<td>Leonhardt et al. (2006)</td>
<td>39</td>
<td>37</td>
<td>PS deficiency</td>
<td>IV rt-PA</td>
<td>0.9 mg/kg</td>
<td>none</td>
<td>good</td>
<td>normal delivery</td>
<td>good</td>
</tr>
<tr>
<td>Murugappan et al. (2006)</td>
<td>37</td>
<td>12</td>
<td>MVR</td>
<td>IV rt-PA</td>
<td>0.9 mg/kg</td>
<td>uterus hematoma</td>
<td>NG</td>
<td>medical abortion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>4</td>
<td>PS decreased activity</td>
<td>IV rt-PA</td>
<td>0.9 mg/kg</td>
<td>none</td>
<td>good</td>
<td>medical abortion</td>
<td></td>
</tr>
<tr>
<td>Wiese et al. (2006)</td>
<td>33</td>
<td>13</td>
<td>MVP</td>
<td>IV rt-PA</td>
<td>0.9 mg/kg</td>
<td>none</td>
<td>good</td>
<td>normal delivery</td>
<td>good</td>
</tr>
<tr>
<td>Yamaguchi et al. (2010)</td>
<td>36</td>
<td>18</td>
<td>PC resistance</td>
<td>IV rt-PA</td>
<td>0.6 mg/kg</td>
<td>none</td>
<td>good</td>
<td>normal delivery</td>
<td>good</td>
</tr>
<tr>
<td>Murugappan et al. (2013)</td>
<td>28</td>
<td>16</td>
<td>FV Leiden</td>
<td>IV rt-PA</td>
<td>0.9 mg/kg</td>
<td>none</td>
<td>good</td>
<td>normal delivery</td>
<td>good</td>
</tr>
<tr>
<td>Hori et al. (2013)</td>
<td>35</td>
<td>14</td>
<td>PS deficiency</td>
<td>IV rt-PA</td>
<td>0.6 mg/kg</td>
<td>none</td>
<td>good</td>
<td>cesarean section</td>
<td>good</td>
</tr>
<tr>
<td>Elford et al. (2002)</td>
<td>28</td>
<td>1</td>
<td>ovarian hyper-stimulation</td>
<td>IA rt-PA</td>
<td>15.5 mg</td>
<td>hematoma</td>
<td>NG</td>
<td>normal delivery</td>
<td>good</td>
</tr>
<tr>
<td>Johnson et al. (2005)</td>
<td>39</td>
<td>37</td>
<td>PS deficiency</td>
<td>IA rt-PA</td>
<td>15 mg</td>
<td>none</td>
<td>good</td>
<td>normal delivery</td>
<td>good</td>
</tr>
<tr>
<td>Murugappan et al. (2013)</td>
<td>43</td>
<td>37</td>
<td>AT3, PC, and PS deficit</td>
<td>IA rt-PA</td>
<td>21 mg</td>
<td>none</td>
<td>good</td>
<td>normal delivery</td>
<td>good</td>
</tr>
<tr>
<td>Li et al. (2012)</td>
<td>24</td>
<td>11</td>
<td>PFO, pAVF</td>
<td>IA rt-PA</td>
<td>NR</td>
<td>recurrence at 2 wks</td>
<td>NG</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Murugappan et al. (2013)</td>
<td>28</td>
<td>6</td>
<td>PFO, PC and PS deficit</td>
<td>IA UK</td>
<td>0.6 MU</td>
<td>buttock bleed</td>
<td>NG</td>
<td>normal delivery</td>
<td>good</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>T1</td>
<td>IE</td>
<td>local UK</td>
<td>0.7 MU</td>
<td>asymptomatic ICH</td>
<td>good</td>
<td>spontaneous abortion</td>
<td>chromosome aberration</td>
</tr>
<tr>
<td>Yamada et al. (2010)</td>
<td>34</td>
<td>39</td>
<td>LAA</td>
<td>local UK → PTA</td>
<td>0.6 MU</td>
<td>none</td>
<td>good</td>
<td>cesarean section</td>
<td></td>
</tr>
</tbody>
</table>


Table 2 Reported cases of acute revascularization therapy for stroke during pregnancy

4 in the 3rd, 8,13,20,22,26,27,31,44,46–50 Including 3 from Japan, 20,49,50 have undergone acute revascularization therapy during pregnancy (Table 2). Nine patients had coagulopathy, three had valvular disease, two had right-to-left shunt, and one each had infectious endocarditis and large artery atherosclerosis. Fourteen of the patients had vessel occlusions in the middle cerebral artery, and one each in the posterior cerebral and basilar arteries. Embolic occlusion was suspected in most cases.

IV rt-PA therapy was administered in nine of the patients; good maternal outcomes were achieved in seven (77.8%), but hemorrhagic infarction and uterine hemorrhage occurred in one each. One patient who underwent angioplasty after IV rt-PA therapy suffered arterial dissection resulting in a fatal outcome. 21 Five healthy babies were born by normal delivery and one by cesarean section, and medical abortion at the 1st trimester was chosen in two cases.

Endovascular therapy was performed in the other seven patients; among these, rt-PA was used in four, and urokinase in three. Maternal outcomes were good in four (57.1%), but hematoma formation occurred in one, buttock hematoma in one, and asymptomatic intracranial hemorrhage in one. Two patients failed to achieve good outcomes due to hemorrhagic complications 13 and ischemic stroke recurrence after 2 weeks. 27 The outcomes of babies were good in four cases with normal delivery and in one with a scheduled cesarean section. One stillbirth (due to chromosome aberration) occurred independent of the revascularization therapy, 31 and the outcome of the seventh was not reported.

Although a publication bias probably exists, because poor results are difficult to publish, no direct adverse effects or complications to either mother or

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baby were observed with acute revascularization therapy during pregnancy. The reported hemorrhagic complications were not life-threatening, and their incidence was also comparable to those observed in non-pregnant women.

**Reports of rt-PA Use During Pregnancy Including Non-stroke Therapy**

There are 28 case reports regarding the use of rt-PA during pregnancy for various types of thrombotic events, including 10 patients with stroke (9 brain infarctions, 7 cerebral venous thrombosis), 7 with thrombosed valve, 7 with pulmonary embolism, 1 with deep vein thrombosis, and 1 with acute myocardial infarction. Maternal outcomes were good for 23 of these patients, 2 died (7%), and 3 experienced hemorrhagic complications (10.7%). This incidence was comparable to that for non-pregnant women. Among the 26 pregnancies (2 mothers died prematurely), fetal outcome was good for 20 of the cases and 6 died (23%). Among the 6 deaths, 3 abortions were performed to give priority to maternal management.

The biggest concern in using rt-PA during pregnancy is the possibility of uterine hemorrhage, resulting in early separation of the placenta. Placental evaluation during the cesarean section in one patient showed 20% separation 12 weeks after the IV rt-PA therapy. Ultrasound evaluation detected the appearance of placental hematoma during IV rt-PA that disappeared after the termination of rt-PA administration. Medical abortion was performed in one patient in whom placental hematoma was detected by ultrasonography during IV rt-PA administration. If rt-PA is administered to pregnant women, adverse effects on embryo-fetal outcome cannot be ruled out. Close cooperation with obstetric specialists is essential to prepare for possible early delivery if necessity. Timing of delivery should be considered and the prognosis for the mother and functional prognosis for the child should be evaluated.

**Discussion**

The problems of acute revascularization therapy during pregnancy can be summarized as follows. First, there are no randomized controlled trials currently available and probably no future trials will be conducted. Therefore, the best level of evidence we have depends on previous case series, and the risks and benefits must be carefully weighed on an individual basis. Second, the uterus and placenta are additional critical organs that present hemorrhagic risk for the mother. Whereas rt-PA does not directly affect the fetus or embryo because of its large molecular size, maternal placental hemorrhage can result in miscarriage or stillbirth. Third, adverse effects for the fetus remain unknown, although animal models have yet to show any teratogenicity of rt-PA.

IV rt-PA administration during pregnancy is controversial among stroke specialists. However, a recent article recommended IV rt-PA therapy for pregnant women if other clinical and imaging factors are favorable. IV rt-PA administration needs to be initiated within 4.5 hours of stroke onset; thus, at the primary stroke center, it is the initial option to save two lives. At a comprehensive stroke center where an angiographic team is available 24/7, endovascular therapy might minimize the risk of bleeding during revascularization therapy, and intensive management can be offered to both mother and baby. A drip-and-ship style strategy would be another option.

**Conclusion**

IV rt-PA therapy is not a contraindication for pregnant women. Acute revascularization therapy using either IV rt-PA or endovascular therapy should be started as soon as possible, depending on availability at the stroke center. Close cooperation with obstetric specialists and intensive care facilities for both mother and child are essential.

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**Conflicts of Interest Disclosure**

The author declares no conflict of interest on this review article.

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