The Use of Tissue Plasminogen-activator in Pregnancy
A Taboo Treatment or a Time to Think Out of the Box
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Acute stroke during pregnancy is an infrequent but a serious and stressful event, not only for the patient but also for healthcare providers. Concerns about the safety of common radiological tests and thrombolytic therapy to the mother and the unborn fetus often lead to the adoption of a conservative do-no-harm approach during this peculiar situation. Clinical trials of thrombolytic therapy in acute ischemic stroke systematically excluded pregnant patients. According to the labeling, recombinant tissue plasminogen-activator (rt-PA) is classified as pregnancy category C, that is, animal studies have shown an adverse effect on the fetus and there are no adequate well-controlled studies in humans. This led many to taboo the use of rt-PA in pregnant patients. Cited concerns often relate to the possible teratogenic effects of rt-PA; the feared effects of thrombolysis on the placenta culminating in premature labor, placental abruption, or fetal demise; and potential medicolegal issues.

Are these fears justified? Yes, but they may be exaggerated. The molecular weight of rt-PA is large (7200 kDa); therefore, it does not cross the placental barrier. Short-term studies in animals have shown no teratogenic effects. According to the package insert, studies that evaluated tumorigenicity of rt-PA in rodents and its mutagenicity and chromosomal aberration assays in human lymphocytes were negative. Although rt-PA decreases the mitotic index, its cytotoxicity is only detected after prolonged exposure at the highest concentrations. Similarly, although rt-PA has been shown to have an embryocidal effect in pregnant rabbits when used intravenously at doses of 3 mg/kg, no maternal or fetal toxicity is evident at 1 mg/kg dosage.

As a result, there have been new insights and experiences in using rt-PA during pregnancy over the past few years. A recent review by Del Zotto et al indicates that thrombolysis for ischemic stroke during pregnancy has been reported in 11 patients. Most were treated during the first trimester, 6 were treated with intravenous rt-PA; 3 with intra-arterial rt-PA; and 2 with urokinase. One patient died; 3 had intracerebral hemorrhage, which was symptomatic in 1 case; 1 had intrauterine hematoma; 2 had an elective abortion; and 1 had a spontaneous miscarriage. No complications were reported in 4 of the 11 patients. The use of thrombolysis in pregnancy has also been reported in other thromboembolic conditions, such as pulmonary embolism, thrombosis of cardiac valve prosthesis, myocardial infarction, and venous embolism. Overall, the reported complication rates were similar compared with nonpregnant patients, with low rates of maternal mortality, fetal loss, and preterm delivery. This led some to question the declared taboo prohibiting the use of rt-PA in pregnant stroke patients, and hence, this controversy.

A quick look at the opinions expressed by our experts reveals that using rt-PA in pregnant patients, who would otherwise be considered candidates for thrombolysis, does not seem debatable. Our opponents both agree that using rt-PA, either systemically or endovascularly, is warranted in our patient.

Opponents of using rt-PA in pregnancy would still argue that the reported experience is limited only to case reports and case series, and that there are no long-term studies in animals to evaluate the carcinogenic potential of rt-PA or its effect on fertility. The effectiveness of rt-PA during pregnancy is also uncertain. There are theoretical reasons to postulate that the thrombolytic efficacy of rt-PA might be impaired during pregnancy. Pregnancy is associated with changes in hemostasis, including a reduction in tissue plasminogen-activator and an increase in plasminogen-activator inhibitors, resulting in an overall hypercoagulable state particularly around term.

Drs Broderick and Demchuk provide important considerations to aid the decision-making regarding the use of rt-PA and its route of administration in pregnant stroke patients. The availability of advanced stroke, endovascular, obstetric, and neonatal facilities and expertise is vital to assure timely management of complications should the need arise. They also highlight the severity of presenting deficits, the extent of potentially salvageable brain tissue, and the location of the vascular occlusion. We add the importance of time once a decision has been made to consider thrombolysis. Time is brain and intravenous rt-PA might be preferable if endovascular intervention is not available in a timely manner. Another factor to consider is stroke pathogenesis. Several conditions during pregnancy can lead to ischemic stroke or stroke-like symptoms,
such as preeclampsia, eclampsia, or amniotic fluid embolism. These conditions are unlikely to respond to thrombolysis. The importance of careful assessment, attempting to ascertain the cause/mechanism of stroke, and confirming the presence of vascular occlusion in these patients before deciding to use rt-PA cannot be understated. The timing of stroke-onset during the course of pregnancy might also influence the decision of whether intravenous rt-PA or endovascular treatment should be considered. Prenatal exposure to large radiation doses and intravenous contrast agents during the early stages of development between weeks 2 and 18 of pregnancy, which might occur during lengthy endovascular procedures, might be associated with increased birth defects and brain injury.

In the absence of randomized controlled trials of thrombolytic therapy during pregnancy, the data from case reports and case series are likely to remain the main source to guide our decision. In our opinion, thrombolytic therapy should not be automatically withheld for potentially disabling stroke during pregnancy, but the risks and benefits must be carefully assessed on a case-by-case basis and discussed with the obstetrician, the patient, and her family; rt-PA should be used only if the potential benefit justifies the potential risk to the fetus.

Disclosures
None.

References

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