The Use of Tissue Plasminogen-activator in Pregnancy
A Taboo Treatment or a Time to Think Out of the Box

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A
cute stroke during pregnancy is an infrequent but a seri-
ous 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 system-
atically 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 medico-
legal 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 embryo-
cidal 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 hemor-
rhage, which was symptomatic in 1 case; 1 had intrauterine
hematoma; 2 had an elective abortion; and 1 had a spontane-
ous 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 prosthе-
sis, 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 oth-
erwise 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 preg-
nancy. 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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