OBSTETRICS

Treatment patterns and short-term outcomes in ischemic stroke in pregnancy or postpartum period

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BACKGROUND: Stroke, which is a rare but devastating event during pregnancy, occurs in 34 of every 100,000 deliveries; obstetricians are often the first providers to be contacted by symptomatic patients. At least one-half of pregnancy-related strokes are likely to be of the ischemic stroke subtype. Most pregnant or newly postpartum women with ischemic stroke do not receive acute stroke reperfusion therapy, although this is the recommended treatment for adults. Little is known about these therapies in pregnant or postpartum women because pregnancy has been an exclusion criterion for all reperfusion trials. Until recently, pregnancy and obstetric delivery were specifically identified as warnings to intravenous alteplase tissue plasminogen activator in Federal Drug Administration labeling.

OBJECTIVE: The primary study objective was to compare the characteristics and outcomes of pregnant or postpartum vs nonpregnant women with ischemic stroke who received acute reperfusion therapy.

STUDY DESIGN: Pregnant or postpartum (<6 weeks; n = 338) and nonpregnant (n = 24,303) women 18-44 years old with ischemic stroke from 1991 hospitals that participated in the American Heart Association's Get With the Guidelines—Stroke Registry from 2008-2013 were identified by medical history or International Classification of Diseases, Ninth Revision, codes. *Acute stroke reperfusion therapy* was defined as intravenous tissue plasminogen activator, catheter-based thrombolysis, or thrombectomy or any combination thereof. A sensitivity analysis was done on patients who received intravenous tissue plasminogen activator monotherapy only. Chi-square tests were used for categoric variables, and Wilcoxon Rank-Sum was used for continuous variables. Conditional logistic regression was used to assess the association of pregnancy with short-term outcomes.

RESULTS: Baseline characteristics of the pregnant or postpartum vs nonpregnant women with ischemic stroke revealed a younger group who, despite greater stroke severity, were less likely to have a history of hypertension or to arrive via emergency medical services. There were similar rates of acute stroke reperfusion therapy in the pregnant or postpartum vs nonpregnant women (11.8% vs 10.5%; $P = .42$). Pregnant or postpartum women were less likely to receive intravenous tissue plasminogen activator monotherapy (4.4% vs 7.9%; $P = .03$), primarily because of pregnancy and recent surgery. There was a trend toward increased symptomatic intracranial hemorrhage in the pregnant or postpartum patients who were treated with tissue plasminogen activator, yet no cases of major systemic bleeding or in-hospital death occurred, and there were similar rates of discharge to home. Data on the timing of pregnancy, which were available in 145 of 338 cases, showed that 44.8% of pregnancy-related strokes were antepartum, that 2.8% occurred during delivery, and that 52.4% were during the postpartum period.

CONCLUSIONS: Using data from the Get With the Guidelines-Stroke Registry to assemble the largest cohort of pregnant or postpartum ischemic stroke patients who had been treated with reperfusion therapy, we observed that pregnant or postpartum women had similarly favorable short-term outcomes and equal rates of total reperfusion therapy to nonpregnant women, despite lower rates of intravenous tissue plasminogen activator use. Future studies should identify the characteristics of pregnant and postpartum ischemic stroke patients who are most likely to safely benefit from reperfusion therapy.

Key words: ischemic, pregnancy, stroke

Stroke is a rare but devastating event during pregnancy or the postpartum period that has been implicated in approximately 7% of United States and 14% of United Kingdom pregnancy-related maternal deaths.[1,2] Because obstetricians are frequently the first point of medical contact for women with stroke symptoms, it is vital that all obstetricians be comfortable recognizing and initiating management for this maternal complication. Whereas intracerebral hemorrhage is the frequently highlighted subtype of pregnancy-related stroke, particularly in the setting of preeclampsia/eclampsia,[2-7] ischemic stroke accounts for approximately 50% of pregnancy-related stroke.[8,9]

Intravenous thrombolysis is a guideline-recommended treatment for ischemic stroke in eligible adults, yet until recently, pregnancy and obstetrical delivery were identified as conditions with potential increased risk in the Food and Drug Administration labeling of alteplase tissue plasminogen activator (tPA).[10] In addition, tPA has been historically categorized as a class C drug in pregnancy, which indicates that animal studies have found some adverse pregnancy-related effects with a paucity of human data.[10] Recent clinical trials have demonstrated positive outcomes with catheter-based acute stroke reperfusion therapy in the setting of adults with ischemic stroke[11-15]; however, pregnant women have been systematically excluded from these and other randomized controlled trials of acute stroke reperfusion therapy, which has limited evidence on which to base clinical decision-making in this population.

Cite this article as: Leffert LR, Clancy CR, Bateman BT, et al. Treatment patterns and short-term outcomes in ischemic stroke in pregnancy or postpartum period. Am J Obstet Gynecol 2016;214:723.e1-11.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2015.12.016

Recent case reports, reviews, and clinical opinions endorse the use of acute stroke reperfusion therapy in pregnant or postpartum women who otherwise meet criteria for this treatment of acute ischemic stroke.[16-30] Using the largest US Stroke Registry, Get With The Guidelines (GWTG)—Stroke, we sought to determine the frequency of acute stroke reperfusion therapy, the characteristics of treated patients, and the short-term outcomes in pregnant or postpartum vs nonpregnant women with ischemic stroke.

Materials and Methods

The GWTG-Stroke program is a voluntary, observational registry and quality improvement program for patients with acute stroke. Quintiles (Cambridge, MA) is the data collection coordination center for the American Heart Association/American Stroke Association GWTG programs. Duke Clinical Research Institute serves as the data analysis center for GWTG; the included analyses of aggregate deidentified data were approved by the Duke University Medical Center Institutional Review Board. A detailed account of the GWTG methods is described elsewhere.[31] In GWTG-Stroke, the eligibility of all acute stroke admissions is confirmed before chart review, and patient data subsequently are abstracted by trained hospital personnel. Relevant medical history that is associated with stroke risk factors (eg, diabetes mellitus, hypertension) are abstracted from the medical record, including pregnancy in women who are pregnant or within 6 weeks after delivery (postpartum). The principle International Classification of Diseases, Ninth Revision (ICD-9), discharge diagnosis code is also captured.

Case identification and data abstraction

We analyzed patient-level data from 1991 GWTG hospital sites that participated in the GWTG program from 2008-2013. The study sample was all women of child-bearing age (defined as 18-44 years old) who were diagnosed with ischemic stroke in GWTG-Stroke (n = 24,641). Of these, 2585 patients received acute stroke reperfusion therapy. Acute stroke reperfusion therapy was defined as intravenous tPA, catheter-based thrombolysis or thrombectomy, or any combination thereof. Pregnancy, our exposure of interest, was defined, consistent with the ICD-9 coding conventions to include women who were pregnant or <6 weeks after delivery at the time of the index event.[32] The 24,641 women with confirmed ischemic stroke were classified as pregnant or postpartum (n = 338) or nonpregnant (n = 24,303) by a combination of a medical history and ICD-9 discharge codes. Although admission for stroke during pregnancy usually results in a principle ICD-9 code for ischemic or hemorrhagic stroke unmodified by pregnancy (code 430-434.xx), some women are assigned codes that are specific for pregnancy-related cerebrovascular events (code 671.5X or 674.0X). Therefore, we determined that ischemic stroke in a pregnant or postpartum woman was present if (1) a clinical diagnosis of ischemic stroke was confirmed in combination with a medical history of pregnancy in GWTG or (2) a clinical diagnosis of ischemic stroke was confirmed in combination with a principle ICD-9 code for pregnancy-related stroke (code 671.5X or 674.0X). We determined that ischemic stroke in a nonpregnant woman was present if a clinical diagnosis of ischemic stroke was confirmed without a medical history of pregnancy in GWTG and without an ICD-9 code for pregnancy-related stroke (code 671.5X or 674.0X). When the fifth digit modifier of the pregnancy-related ICD-9 codes was present, it provided information on the timing of pregnancy; antenatal hospitalizations are nondelivery admissions during pregnancy (fifth digit modifier 3); delivery hospitalizations include the event of delivery (fifth digit modifier 1 or 2), and postpartum hospitalizations are distinct from delivery hospitalizations and within a window of 6 weeks after delivery (fifth digit modifier 4).

The main analysis cohort was all 2585 pregnant or postpartum and nonpregnant women who received acute stroke reperfusion therapy. Subsequent sensitivity analyses were conducted in all those who received intravenous tPA monotherapy only. *Symptomatic brain hemorrhage* was defined in GWTG-Stroke as a computed tomography within 36 hours that showed intracranial hemorrhage and physicians' notes that indicated clinical deterioration because of hemorrhage.[33] *Life-threatening, serious systemic hemorrhage* was, as per GWTG, defined as bleeding within 36 hours of intravenous tPA and >3 transfused units of blood within 7 days or discharge and physicians' notes that attributed the hemorrhage as the reason for transfusion.

Stroke quality of care and outcomes

We compared the quality of thrombolytic therapy administration between pregnant or postpartum and nonpregnant patients using previously defined evidence-based metrics from the GWTG-Stroke Registry (which included the percentage of tPA-eligible patients with a door-to-needle time; ie, initiation of therapy) for intravenous tPA at ≤60 minutes and the percentage of eligible patients who arrived within 2 hours and were treated within 3 hours of last known to be well (ie, without any stroke symptoms, or at baseline prestroke level of function) with intravenous tPA.[34] We also report the percentage of in-hospital deaths, independent ambulation at discharge, and discharge to home. Length of stay of >4 days was chosen as another discharge outcome because it was the median length of stay for the entire cohort.

Statistical analysis

Patient, hospital characteristics, care delivery metrics, and discharge outcomes were reported for pregnant or postpartum and nonpregnant women with ischemic stroke with the use of proportions for categoric variables and medians with 25th and 75th percentiles (interquartile range) or means with standard deviations for continuous variables. Differences in these characteristics were compared with the use of chi-square tests for categoric row variables and Wilcoxon Rank-Sum for continuous row variables.

Conditional logistic regression was used to assess the association of