Decision Making and the Limits of Evidence: A Case Study of Acute Stroke in Pregnancy

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Abstract

We report the case of a pregnant woman treated for acute ischemic stroke and review the literature on acute stroke treatment in pregnancy. To our knowledge, this is the first case reporting the successful use of intravenous tissue plasminogen activator and a stent retriever for acute stroke in pregnancy. We then use this case to consider the way medical knowledge is used in therapeutic decision making and argue that decision making necessarily extends beyond the limits of clinical trial evidence.

Keywords

acute stroke, therapy, pregnancy, evidence, decision making

Introduction

Ischemic stroke is fortunately a rare occurrence in pregnancy. However, when it does occur, neurologists can be faced with difficult therapeutic decisions. Specifically, how should neurologists select among therapeutic options when clinical trial data are lacking? In this article, we report a case of acute stroke in pregnancy successfully treated with intravenous (IV) thrombolysis and stent-retriever thrombectomy, the first reported case of which we are aware. We briefly review the literature on acute stroke treatment in pregnancy and consider the way therapeutic decision making occurs in the absence of evidence from randomized clinical trials (RCTs).

The Case

Mrs R is a 32-year-old woman, Gravida 4 Para 2 (G4P2), at 37 weeks gestation who arrived in the emergency department approximately 50 minutes after developing right-sided weakness and global aphasia. The heart rate was 127, and the blood pressure was 134/87. Neurological examination demonstrated that the patient was mute but was able to follow some commands, with right hemiparesis and hemisensory loss. Her initial National Institutes of Health Stroke Scale (NIHSS) score was 16, consistent with a significant clinical deficit.

A review of her past medical history revealed hypothyroidism, obesity, and obstructive sleep apnea. Her only medication was levothyroxine. She had no known allergies. Laboratory studies were normal.

The unenhanced computed tomography (CT) scan of the head demonstrated a hyperdense left middle cerebral artery (MCA) sign with early ischemic changes in the left lentiform nucleus and insular cortex. The Alberta Stroke Program Early CT Score (ASPECTS) was 8, suggesting minimal completed infarction. A CT angiogram demonstrated a sharp occlusion in the first (M1) segment of the left MCA with good collateral circulation (Figure 1).

Knowledge, Evidence, and Treatment

The incidence of ischemic stroke in pregnancy is difficult to quantify, with estimates varying from 4 to 40 per 100 000 pregnancies.¹ It is controversial to what degree pregnancy should be considered a risk factor for stroke in and of itself.^{2,3} Mechanisms of stroke in pregnancy and the puerperium may reflect common processes (smoking and hypertension) or rarer processes such as postpartum cardiomyopathy, coagulopathies, and vasculopathies.⁴

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Figure 1. Unenhanced CT, CT angiogram and CT perfusion on presentation. A, Unenhanced CT scan of the head demonstrates early ischemic change in the insular cortex and lentiform nucleus, giving an ASPECTS score of 8. B, Contrast-enhanced CT angiogram shows occlusion of the left middle cerebral artery in the mid-M1 segment. C, Cerebral blood volume is decreased in the region of the lentiform nucleus, consistent with the hypodensity seen on unenhanced CT. D, Mean transit time is prolonged throughout the left MCA territory. CT indicates computed tomography; ASPECTS, Alberta Stroke Program Early CT Score; MCA, middle cerebral artery.

Therapeutic options for ischemic stroke in pregnancy are similarly controversial. Seminal trials that investigated the use of tissue plasminogen activator (tPA), the only therapy currently approved for acute ischemic stroke, explicitly excluded pregnant patients.⁵ The major complication associated with the use of thrombolytics is hemorrhage, be it intracranial, gastrointestinal, or intrauterine. Tissue plasminogen activator does not cross the placenta but may precipitate placental hemorrhage, which would be the major complication specific to a pregnant patient population.¹

To date, only a small number of reported cases have detailed the use of IV tPA in pregnancy and the puerperium.^{6,7,8,9} Of 6 reported cases, 1 patient died, 1 had minor hemorrhagic transformation of the infarct, and 1 had an intrauterine hematoma; in 3 cases the pregnancy was lost or was terminated.¹ Among 28 pregnant patients who received thrombolysis for any thromboembolic process, the cumulative risk of death was 7% and the risk of fetal demise for any reason was 24%.⁹ Despite the absence of randomized trial data to support the use of thrombolytics in pregnancy, several leading experts have advocated that “thrombolysis should be considered for all potentially disabling strokes during pregnancy,”

(p. 88)¹ arguing that the “risk is low and the likelihood of benefit from IV tPA significant.”¹⁰

Pregnant patients have also been excluded from recent and ongoing trials of intra-arterial stroke therapy (thrombolysis and mechanical thrombectomy), and there are no published experiences on the use of modern mechanical thrombectomy devices for ischemic stroke during pregnancy.^{11,12,13,14} However, endovascular therapy can be successful with lower doses of thrombolytic agents or none at all,¹⁵ as in the case of the latest generation of stent retrievers. Several case reports have outlined the uses of intra-arterial thrombolytics for the treatment of stroke in pregnancy without complications.^{16,17,18} However, endovascular management is not without risk, and 1 pregnant patient is reported to have died due to iatrogenic intracranial dissection during attempted administration of intra-arterial tPA.⁸ At the time of this patient’s presentation, no positive clinical trials had yet been published to support stent-retriever thrombectomy, though the clinicians involved had been active recruiters into several endovascular trials.

Treatment Decisions

Therapeutic options in this case included no acute therapy, IV thrombolysis with tPA, intra-arterial clot removal with a modern stent retriever, or a combination of IV and intra-arterial therapies. The obstetrical team was consulted, and they advised that medical management should prioritize the mother’s health. The initial reaction of the neurologist on call was to prefer intra-arterial over IV therapy in this case, reflecting the lack of randomized trial data for IV tPA in pregnancy and concerns about hemorrhage related to the use of systemic thrombolytics in this population. Granted, there was an equivalent lack of clinical trial evidence for the use of intra-arterial thrombectomy in pregnancy. Moreover, there was as yet no randomized trial data supporting endovascular stroke therapy at the time this decision was being made.

In addition, both neuroangiography suites in the institution were occupied by patients undergoing procedures, and the start of an intervention on Mrs R would be delayed. The interventional neuroradiologists consulted on the case anticipated that the procedure would be challenging, given the patient’s body habitus and the anatomy of her aortic arch. Therefore, the neurologist on call considered administering IV tPA while awaiting endovascular therapy. This option was discussed with a second staff neurologist and with Mrs R.’s husband. He was distressed but agreed to pursue both therapies should they be necessary.

Intravenous tPA was administered 49 minutes after the patient’s arrival in the emergency department and 1 hour 39 minutes after symptom onset. Endovascular therapy began during the tPA infusion, and partial recanalization of the occluded MCA was achieved after the first pass of a Trevo stent retriever approximately 2.5 hours after symptom onset. After a second pass with the device, an excellent angiographic result (Tici-3a flow) was obtained (Figure 2).

Figure 2. Digital subtraction angiogram, pre- and post-stent retriever. A, Coronal view of a left internal carotid artery (ICA) injection demonstrates occlusion of the mid-M1 segment. Collateralization is provided from the left anterior cerebral artery. B, Sagittal view of the left ICA injection again demonstrates lack of opacification of the left middle cerebral artery (MCA) branches. C, Coronal view with contrast injection in the terminal ICA demonstrates restoration of flow (Tici-3a) in the left MCA territory. D, Sagittal view shows opacification of the MCA branches beyond the M1 segment.

Immediately postprocedure, Mrs R demonstrated only mild right facial droop, with an NIHSS score of 1. A fetal ultrasound was normal. The patient was admitted to the intensive care unit, where she remained neurologically stable. A magnetic resonance imaging (MRI) scan performed the next day demonstrated areas of subacute infarction in the left insula and left lentiform nucleus, consistent with the areas of hypodensity on the initial CT scan. There was also mild irregularity in the distal M1 artery suspicious for dissection and some hyperintensity in the convexity subarachnoid space on T2 and Fluid Attenuated Inversion Recovery (FLAIR) but not on Gradient Echo (GRE) sequences. A repeat MRI 2 days later demonstrated no change in the appearance of the artery (Figure 3), although there was now blooming on SWI in some of the regions where sulcal hyperintensity had previously been noted, suggestive of subarachnoid hemorrhage.

Due to concerns about the possibility of an iatrogenic intracranial dissection, plans were made for Mrs R to deliver her baby via cesarean section. One week after her stroke, Mrs R

gave birth to a healthy baby girl. She was prescribed aspirin 81 mg daily for secondary stroke prevention and has had no further neurological events. Investigations of stroke etiology have failed to reveal a specific cause. The MCA appears normal on MR angiography at 3 months.

Decision Making and the Limits of Evidence

This case report describes the first known use of stent retrievers in a pregnant patient with acute ischemic stroke. The clinical and radiologic success of our case, in the face of an M1 occlusion and severe clinical deficits, aligns with the growing literature in favor of the use of stent retrievers for acute, proximal, and large artery ischemic stroke.^{19,20,21} We feel that this case augments that literature by reporting the efficacy of stent-retrievers in a patient population that was explicitly excluded from those clinical trials. Moreover, we believe this case suggests interesting questions about the process of medical decision making. Specifically, how does physician decision making proceed when evidence from randomized trials is not

Figure 3. Follow-up MRI scan, post-stroke day 2. A, FLAIR sequence demonstrates hyperintensity in the lentiform nucleus and insular cortex, consistent with subacute infarction. Hyperintensity in the cortical sulci suggests subarachnoid hemorrhage. B, There is hyperintensity in the lentiform nucleus and insular cortex on diffusion-weighted imaging, as well as hypointensity suggestive of localized hemorrhage in those same regions. C, Time-of-flight MR angiogram demonstrates recanalization of the left MCA, albeit with some focal irregularity of the M1 segment. The right A1 segment appears congenitally absent. MRI indicates magnetic resonance imaging; MCA, middle cerebral artery.

available, and how does this differ from cases in which RCT evidence is available?

A large literature on medical decision making has developed in recent decades,^{22,23,24} most of which has focused on better integrating patients and families into the decision-making process.^{25,26,27} In acute stroke care, the urgency of decision making and the extent to which patients are often incapacitated means that most decisions are made predominantly by the physicians involved.²⁸ Physician decision making has been studied using quantitative methods adapted from mathematics and economics,^{29,30} as well as using qualitative approaches built on historical, philosophical, and psychological principles.³¹⁻³⁵

On a very basic level, physician decision making tends to reflect the influence of some collection of *knowledge* and some set of *values*.^{28,31,36} For example, physician opinions about which treatment is most appropriate for a given clinical condition will be based on beliefs about treatment efficacy and beliefs about what qualifies as a meaningful clinical outcome.²⁸ Over the course of the last 20 years, physicians throughout much of the developed world have come to accept the principles of evidence-based medicine, which consider the best determinant of treatment efficacy to be knowledge acquired from RCTs and their meta-analyses. This type of knowledge is commonly called “evidence.”³⁷

However, in many cases, clinical trial evidence is lacking. Pregnant patients, the very old, and the very young will likely always be under-represented in clinical trials. The treatment of rare genetic diseases is also unlikely to ever be informed by large, multicenter randomized trials. In other diseases that show significant anatomic or physiologic variability, population-based determinations of efficacy and outcome may be insufficiently specific. Arguably, the vast majority of clinical scenarios do not yet benefit from direct RCT evidence and

may never do so. Decision making in the absence of clinical trial evidence is not the exception but the rule.

In the absence of RCT evidence, decision making still depends upon knowledge of physiology and experimental medicine, of case reports, and of related trials, interpreted in a context informed by a clinician’s experiences and values. In our case, the decision to offer both IV tPA and mechanical thrombectomy was based upon belief in the importance of rapid revascularization, upon knowledge of treatments supported by clinical trials and experience, upon our aim of achieving a return to health for the patient as well as upon consideration of her age, anatomy, and severity of deficit. These factors were framed by recognition of available services and by the patient’s husband’s support for all measures that might restore her to health.

In the absence of knowledge from clinical trials, decision making would appear to be an integrative and evaluative process, exemplified by our case of acute stroke treatment in pregnancy. However, we contend that physician decision making in the presence of RCT evidence is not fundamentally different. Although advocates of evidence-based medicine claim that RCT evidence “implies a clear course of action for physicians,” (p. 8)³⁷ RCTs do not eliminate the interpretive aspect of physician decision making. While RCT data are very important in modern clinical decision making, they can only speak to the optimal treatment for a population of patients and do not guarantee the outcome of a given intervention for any given patient. In any clinical trial, some patients in each arm will do well and some will not. Recent empirical studies of the treatment of acute stroke patients have demonstrated how decision making requires more than blindly following clinical trial evidence: physician beliefs, values and uncertainties play a part, and must do so.³⁸ Calls that physicians should

“recognize when and why they are making value judgments rather than clinical judgments,”³⁹ and excise such value judgments from their decision making, fail to capture the realities of clinical practice. Even in the presence of clinical trial evidence, decision making requires an evaluation of available knowledge in light of risks, benefits, and potential outcomes for the specific patient in question. Any consideration of risks and benefits means that values—those of the patient, physician and society—are necessarily incorporated into the decision-making process. How physicians make decisions when no clinical trial data are available, we suggest, is no different from what they do in all other circumstances. As in this case of acute stroke treatment in pregnancy, physician decision making is a complex process that necessarily extends beyond the limits of clinical trial evidence.

Declaration of Conflicting Interests

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