First Trimester Stroke Prophylaxis in Pregnant Women With a History of Stroke

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Background and Purpose—Current recommendations for stroke prevention during early pregnancy in women with a prior stroke history are based on limited evidence. In view of the uncertainty involved in balancing the fetal risk of medication against the maternal risk of recurrent stroke, a substantial variation in clinical decision making was anticipated. Thus, a survey was performed to describe the current practices of U.S. neurologists with a particular interest in stroke with regards to treatment of such patients.

Methods—A survey was sent to 384 actively practicing U.S. members of the American Academy of Neurology Stroke and Vascular Neurology section asking what antithrombotic, if any, they would use during first trimester pregnancy in women with a prior history of stroke, either unrelated or related to a previous pregnancy.

Results—230 practitioners responded. Some form of antithrombotic therapy was selected by 75% of practitioners for women with a history of prior stroke not related to pregnancy and by 88% of practitioners for women with a history of prior stroke related to pregnancy. Aspirin and low molecular weight heparin were chosen by 51% and 7%, respectively, for stroke unrelated to pregnancy and by 41% and 25%, respectively, for stroke related to pregnancy.

Conclusions—Most practitioners agree that women with a history of stroke should receive prophylaxis during the first trimester. However, much disagreement exists regarding which drug(s) to use. A national registry would be the most practical method of obtaining maternal and fetal outcome data to guide practice in this setting. (Stroke. 2009;40:1158-1161.)

Key Words: all cerebrovascular disease/stroke ■ stroke in young adults ■ stroke prevention

Based on data from the 2006 National Health Interview Survey, an estimated 253,000 women 18 to 44 years of age, or nearly 1 in 200 women of childbearing age, reported being told by a health professional that they had had a stroke.1 Thus, a relatively common clinical question is what antithrombotic therapy should be recommended in a young woman with prior ischemic stroke or transient ischemic attack who is considering pregnancy. To answer this question the clinician must balance the risk of stroke occurrence or recurrence to the mother against risk of adverse effects to fetus and mother. The choice of therapy is most difficult during the first trimester when the risk of teratogenicity is highest.

Present American Heart Association recommendations state “Pregnant women (with noncardioembolic stroke) may be considered for treatment with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) in the first trimester, followed by low-dose aspirin for the remainder of the pregnancy.”2 Recommendations for injectable heparins, however, are based on class IIb, level C evidence, and also do not take into account the burden and expense of daily injections. Given the limitations of the evidence available to guide stroke prophylaxis during the first trimester, we performed a survey to describe the current practices of American neurologists with a particular interest in stroke.

Methods

After excluding inactive, international, and otherwise ineligible candidates, we emailed a 1-page questionnaire to all 384 members of the American Academy of Neurology Stroke and Vascular Neurology section who were practicing neurologists. In addition to demographic data, the survey instrument asked two questions: (1) What is your current practice (or would be your choice) for stroke prophylaxis during the first trimester in a pregnant woman with a past history of noncardioembolic ischemic stroke not related to pregnancy? (2) What is your current practice (or would be your choice) for stroke prophylaxis during the first trimester in a pregnant woman with a past history of noncardioembolic ischemic stroke related to pregnancy? Respondents chose from a list of possible treatments (see Table) or could fill in another choice. Respondents were also given a space for open comments.

Responses were collected and tabulated by the AAN Surveys and Research Department. Answers to the two treatment questions were examined in relationship to demographic data to elucidate patterns of
practices. Two-sided probability values were calculated using Fisher exact test with no corrections for multiple comparisons.

**Results**

Two hundred and thirty questionnaires were returned for a response rate of 60%. 50% of respondents had done a stroke fellowship or had vascular neurology certification. Nearly half (44%) stated they saw 6 or more women of childbearing age per year for a diagnosis of stroke or TIA. 70% had been in practice for more than 10 years. 41% stated that more than half of their practice comprised cerebrovascular disease. Practice types are represented in Figure 1.

Figure 2 shows the responses for first trimester stroke prophylaxis in a woman with a nonpregnancy related stroke history. The most common choices were 81 mg aspirin or no treatment during the first trimester, which together accounted for two thirds of responses. Aspirin in any dose accounted for greater than half of responses. Subgroup analysis showed that practitioners who saw at least one pregnant woman per year requiring stroke prophylaxis were more likely to choose some form of antithrombotic medication than those who rarely or never saw such patients, 81% versus 58% ($P=0.0006$). Additionally, respondents with stroke fellowship or Vascular Neurology certification were more likely to give some form of antithrombotic than those without, 86% versus 65% ($P=0.0003$). The same group also showed a trend toward choosing clopidogrel, 8% versus 3% ($P=0.14$). Neurologists in practice less than 5 years were similarly more likely to choose clopidogrel, 18% versus 4% ($P=0.02$), compared to those who were in practice longer.

The responses for treatment preference for first trimester stroke prophylaxis in women with a history of stroke related to pregnancy are shown in Figure 3. The responses showed a higher rate of treatment overall at 88%, compared to 75% overall in nonpregnancy related stroke. Once again, the most common choice was 81 mg aspirin, and any dose of aspirin accounted for nearly half of respondents’ preferences. The second most common selection, however, was LMWH, with any form of heparin accounting for nearly one third of responses. Subgroup analysis showed that there was no significant difference in the likelihood to use any form of antithrombotic between those who see at least one woman per year versus those who rarely or never see such patients, 90% versus 83% ($P=0.17$). However, there continued to be a higher use of any form of antithrombotic by those with stroke fellowship or vascular neurology certification, 93% versus 84% ($P=0.04$). They were also more likely to use LMWH or UFH than those without such fellowship or certification, 37% versus 25% ($P=0.06$). Once again, those in practice less than 5 years were more likely to choose clopidogrel, 14% versus 2% ($P=0.03$).

Several respondents commented that they had difficulty answering the questions because the questions did not give enough information and that their treatment choices would depend on the stroke mechanism.
It is clear from the results of this survey that there is no consensus among U.S. practitioners on the optimal therapy for stroke prevention during early pregnancy in women with a history of stroke. It is not surprising that practices varied greatly because the teratogenic risk of several prophylactic medications is not well characterized and the risk of stroke recurrence during pregnancy is not known with precision. It is known that the risk of initial stroke during the first trimester of pregnancy is not increased compared to the nonpregnant state. The risk of recurrent stroke during the first trimester might also be assumed to be low compared with late pregnancy or the postpartum period, but has not specifically been studied. The French Study Group on Stroke in Pregnancy looked at the risk of recurrent ischemic stroke among women who did or did not become pregnant after stroke. The point estimate for the yearly recurrence rate was 0.5% outside of pregnancy and 1.8% for the entire pregnancy and the postpartum period. The best estimate of the risk difference between women who did and did not go on to have a subsequent pregnancy was about 1.3%. However, the wide 95% confidence intervals include the possibility that the true excess risk is as great as 7.5%. There were no questions in the survey to assess respondents’ understanding of these risks, and several respondents in this survey commented specifically that more information on recurrence risk was needed to help guide them in therapy choices regarding these patients.

The high proportion of practitioners who stated they would place such patients on some form of therapy suggests a general consensus that the risk of recurrence is high enough to merit the risk of therapy. The survey responses suggest that use of antithrombotics would be more frequent in this U.S. sample than use in the French study (75% to 88% versus 56%). It is not clear whether this is attributable to real differences in practice patterns or is attributable to response or sample selection bias. The survey responses also suggest that practitioners feel that the risk of recurrence is higher in those with a history of pregnancy-related strokes because choice of an active treatment was higher for such patients (88% versus 75%).

The choice of antithrombotics was also interesting. In some cases, the choice was clearly based on FDA pregnancy ratings. Clopidogrel, which was more commonly chosen by the recently trained or those with fellowship or vascular certification, carries a rating of “B.” One respondent specifically stated in a comment that this was the reason for his/her choice of clopidogrel. A “B” rating is based on animal studies with no fetal risk but no controlled human studies, or controlled human studies which did not confirm animal studies showing fetal risk. The “B” rating of clopidogrel is based on animal studies alone, and it is not known whether the drug crosses the human placenta. There are only a few case reports of studies in rabbits and rats suggesting that there is no fetal toxicity; however, no human studies have been performed so far. There are only a few case reports of women who had a successful pregnancy while taking clopidogrel. Miscarriage rates have also not been reported. Given that lack of efficacy data of clopidogrel in prevention of stroke during pregnancy, the pregnancy rating probably accounts for its use. It is not clear why more recent trainees were more likely to make this choice.

LMWH is also category “B,” based on both animal and human safety data. It does not cross the placenta and has a low miscarriage rate. There is also extensive experience with its use during pregnancy in women with a history of thromboembolism. UFH carries category “C.” This difference in FDA rating may explain why LMWH was chosen in this study 3 to 4 times more often than UFH despite being equally recommended by the AHA. There are also other benefits of LMWH over UFH including better bioavailability, more predictable pharmacokinetics, and longer plasma half-life as well as less risk of severe side effects such as osteoporosis, and heparin-induced thrombocytopenia.

The high rates of aspirin use, however, were clearly not based on FDA pregnancy rating. Aspirin carries a category “D” rating. A “D” rating states that there is positive evidence of human fetal risk, but in some circumstances, the benefits may outweigh the risks. Available evidence suggests that low-dose (less than 150 mg/d) aspirin during the second and third trimesters is safe for both mother and fetus. Case-control studies have suggested a possible association with several rare conditions. One study has found an association between aspirin use of unspecified dose during the first trimester and persistent pulmonary hypertension in the newborn. An association between first trimester aspirin use and gastroschisis has been found in some but not all studies. There is also concern that use of aspirin close to delivery, particularly at high doses, could cause premature closure of the ductus arteriosus. Despite these potential risks, low dose aspirin is considered to be relatively safe and to have generally positive effects on reproductive outcomes. The experience of the prescribers, low cost, and ease of use may also have contributed to aspirin being the most popular choice for secondary prevention of ischemic stroke during the first trimester.

This survey does have several limitations. First, as many respondents to the survey noted, the responses were constrained by the design of the questionnaire. Respondents were unable to take into consideration specific risk factors, the mechanism of prior strokes, or maternal attitudes toward risk in these theoretical patients. Indeed, the most frequent comment was that the answers would depend on the specifics of the clinical situations.

There are also limitations to the generalizability of the results of this survey. The sample was restricted to U.S. neurologists who have a particular interest in stroke as evidenced by membership in the stroke section of the AAN. Thus, this may not allow generalization to all practitioners who may encounter such patients, particularly general neurologists, or obstetricians. Additionally, some of the subgroup analyses may be limited by lack of precision because of small numbers, eg, use of clopidogrel by those recently completing training. Although this study had an excellent response rate of 59.9%, compared to an average response of 40% to 50% for surveys by the AAN Surveys and Research Department, there may also have been a nonresponse bias as we do not have information regarding the 40% of practitioners who did not return the survey.
The results of this study suggest that the FDA labeling system for drug safety in pregnancy may have been misinterpreted by physicians, and that further study is warranted as there are few data and no consensus on the safety and effectiveness of therapies in early pregnancy. Two measures may help improve the future care of women in early pregnancy who have had a prior ischemic stroke. First, the FDA is proposing elimination of the letter category system and substituting a risk summary and more detailed information about available data on use of the drug during pregnancy and while breastfeeding. Second, more data are needed. The optimal study design, a randomized study, is not likely to be feasible because of the heterogeneity of clinical circumstances, the sensitivity of intervention studies in pregnant women, and the exceptionally large sample sizes that would be required to detect differences in efficacy between agents. Thus, we recommend the institution of a nationwide registry to record patient history, treatment choices, and maternal and fetal outcome as an alternative method to gain further information about the risks and benefits of antithrombotic agents in early pregnancy.

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Disclosures
O.D. is a salaried employee of the American Academy of Neurology.

References
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