Expert Opinion

Migraine With Aura During Pregnancy

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An increasing frequency of migraine with aura during pregnancy raises a variety of interesting questions.

CLINICAL HISTORY

This is a 38-year-old G2 right-handed woman seen at 28 weeks gestation for headaches. At the age of 13, she started having migraines with aura that were frequent for several years and then became less so for many years. During her prior pregnancy 3 years ago, she had 3 migraines with aura. She had no other similar headaches until 2 months ago. She reports 9 episodes with 4 occurring during the prior 2 weeks. Her typical aura involves "squiggles" with scotoma in both eyes for about 30 minutes, no symptoms for 30 minutes, then the same visual symptoms again for 30 minutes followed by a severe bitemporal headache associated with nausea and light sensitivity; her headaches resolve a few hours after taking a butalbital/APAP/caffeine compound and sleeping. She is not aware of any migraine triggers. The last 4 episodes have been different. She develops the same visual aura for 30 minutes, then no symptoms for about 30 minutes, and then the same visual aura but now accompanied by numbness of the fingers of the left hand spreading up the forearm and then to the left forehead, cheek, and lips. The visual and sensory symptoms resolve in about 30 minutes and are then followed by her typical headache.

Past medical history is otherwise unremarkable. Her father had migraine. Her blood pressure and neurologic examination were normal.

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Questions.—How often does migraine with aura become more frequent during the second and third trimesters? Is there any significance to the new sensory symptoms occurring with the visual aura? Is diagnostic testing indicated? Would you recommend migraine preventative medication, and, if so, which one?

EXPERT COMMENTARY

In both of her pregnancies, this patient has experienced a worsening of headache compared with her immediate prepregnancy baseline. Is this coincidental, or might it be causally related in some way to pregnancy? Hormonal factors are widely believed to influence the course of migraine, and much evidence suggests that for most women, migraine is likely to improve during pregnancy. For example, the large Collaborative Perinatal Project, collecting data on over 55000 pregnancies, suggested that 17% of women identified as having migraine experienced complete cessation of headache in pregnancy, with 62% experiencing 2 or fewer headaches in the last trimester.[1] In their sample, only 21% of women experienced no improvement. Many factors limit the generalizability of this study, however, including the unusually low (2%) prevalence of identified migraine at the first prenatal visit. Unfortunately, most studies examining the course of migraine in pregnancy are retrospective. In a prospective study, Marcus et al found that 61% of women with migraine experienced either no improvement or worsening, of headache in pregnancy.[2] In particular, an ameliorating effect of pregnancy may be less likely in migraine with aura than in migraine without aura. Cupini and colleagues found a similar

course for migraine with and without aura in pregnancy, but a more careful and systematic study by Granella et al found that headache improvement during pregnancy occurred in only 43% of patients who had migraine with aura, compared with 72% of patients who had migraine without aura.[3,4] What might account for the fact that migraine does not improve with pregnancy, or the differential influence of pregnancy on migraine with versus without aura?

A number of factors may play a role. First, it is possible that high levels of estrogen have a disproportionately negative effect on migraine with aura compared with migraine without aura. Somerville's work in the early 1970s suggested that falling estrogen levels were the provocative factor in menstrually triggered migraine, but he did not attempt to distinguish between migraine with and without aura. By extension from his work, it might be theorized that the high, stable estrogen levels of pregnancy exert a moderating effect on the disorder. Even so, it seems possible that high levels of estrogen in fact have a differential effect on the two types of migraine. MacGregor has reported worsening of migraine with aura in women on hormone replacement, with improvement when the replacement therapy is stopped or the dose of estrogen lowered.[5] Consistent with this hypothesis is Cupini's observation that when migraine began for the first time in pregnancy, it was more likely to be migraine with aura than migraine without aura.[3]

Second, affective disorders are known to be more common in patients who have migraine with aura compared with those who have migraine without aura, who in turn have higher levels of affective disorders than controls.[5] Stressful events and disrupted sleep are known to be triggers of headache[6]; it is not unreasonable to suppose that the higher burden of comorbid affective and mood disorders in migraine with aura, acting in combination with the stress of pregnancy, may explain why fewer of these patients improve during pregnancy. In support of this possibility, the retrospective case-controlled study by Granella mentioned previously also suggested that a prior history of menstrual migraine was less common and premenstrual syndrome more common in patients who had migraine with aura than in those who had migraine without aura.[3] If, as seems likely, premenstrual syndrome is a form of affective illness, this latter observation is consistent with the higher prevalence of affective disorders in migraine with aura.

Third, the high estrogen levels of pregnancy are known to enhance platelet aggregation and thrombosis. The importance of platelet aggregation in migraine is controversial, but some evidence suggests that there are differences in platelet aggregability in migraine with aura compared with migraine without aura.[7,8] In addition, platelet aggregation seems to be more marked in sufferers of hormonally mediated headaches.[9] If platelet aggregation does play a more important role in migraine with aura and hormonally activated headaches, it is possible that the high estrogen levels of pregnancy, which enhance platelet aggregation, have a differential influence on the frequency of headache in patients who have migraine with aura compared with those who have migraine without aura.

Fourth, at least one report suggests that previously undetected right-to-left cardiac shunts are more common in divers who have migraine with aura, and that factors that act to increase the size of the shunts (such as diving) are associated with an increased risk of attacks.[10] If this is true of migraine with aura sufferers in general, in at least some patients with migraine with aura who have right-to-left shunts, the increased right-sided venous pressures associated with pregnancy might act to worsen shunting and thus migraine.

Finally, the hormonal milieu is only one of many factors that influence susceptibility to migraine. In some women with migraine, other influences that have a negative effect on headache frequency may act in opposition to any stabilizing hormonal changes during pregnancy. Much of the above is speculation, not fact, but illustrates how it might be that migraine with versus without aura, despite their clinical similarities, are differently affected by pregnancy and why not all pregnant migraineurs experience headache improvement. These explanations are not mutually exclusive and represent only a few of the many aspects of the two disorders that may, in various combinations, account for the differences we observe clinically among patients.

In addition to a general worsening of migraine during her second pregnancy, this patient experienced a change in the character of her aura symptoms, with additional symptoms of left hand numbness and facial tingling and a more stuttering course. The "cheiro-oral" distribution and gradual evolution of her symptoms are highly characteristic of migraine aura and reassuring that serious underlying pathology is unlikely. Also in support of a benign cause of this patient's symptoms are her rapid recovery from the episodes, normal interictal neurologic status, and the presence of the reassuring "positive" visual phenomenon of "squiggles." Faced with a similar case in a nonpregnant patient, some might consider the use of an antiplatelet agent such as low-dose aspirin. Despite the lack of clear evidence that this is helpful, it is theorized that aspirin-mediated decreases in platelet aggregation might lower the risk of ischemic sequelae from an attack in which pronounced vasoconstriction occurs. Aspirin in late pregnancy can cause premature closure of the ductus arteriosus and contribute to bleeding problems in mother and fetus, and so is probably best avoided in this pregnant patient. Still others might add a calcium channel antagonist, such as verapamil, with the expectation that it would protect against vasoconstriction. The concept of vasoconstriction as a cause of aura, however, is in serious question, and controlled studies supporting this treatment approach are lacking. Calcium blockers also exert a tocolytic effect on uterine musculature, and I would not recommend their use in this patient.[12]

Other causes of headache in pregnancy must be recalled as well. Subarachnoid hemorrhage and cerebral venous thrombosis are both more common in pregnant than nonpregnant patients. Headache can be an early sign of preeclampsia, appearing before the proteinuria and increased blood pressure characteristic of that condition. This patient's intermittent headaches, normal neurologic status between attacks, and reassuring blood pressure readings, however, argue against these as possibilities in this case. For all of these reasons, I do not believe this patient requires an imaging study or further investigation. If sufficient concern did exist regarding a secondary cause of headache, however, the presence of pregnancy should not alter or delay appropriate investigation.

Of direct relevance to the practical aspects of our case study, Marcus has shown that if improvement in headache has not occurred by the end of the first trimester of pregnancy, it is unlikely to occur.[2] Thus, our patient's headaches are likely to remain at their current level for the duration of her pregnancy. She is past the first trimester, when organogenesis occurs and during which it is especially important to avoid unnecessary drug exposure. Most women and their physicians prefer to pursue a conservative course regarding medications throughout pregnancy, and not just during the first trimester. Basic "headache hygiene" measures such as adequate rest, regular meals, and avoidance of other known patient-specific headache triggers are especially important in this situation. Biofeedback has been shown unequivocally to be useful in the treatment of migraine in general,[13] and migraine in pregnancy in particular.[14,15] Ideally, this should be taught and practiced regularly before pregnancy begins. Unfortunately, obtaining insurance coverage for this safer and more appropriate method of headache treatment is frequently difficult, if not impossible; this limits access for many pregnant women who would benefit. The positive effects of a combination of physical therapy, relaxation training, and biofeedback offered to pregnant women with migraine have been shown to persist up to 1 year following pregnancy.[15] Such treatment should be offered to this patient.

This patient's headaches are relatively infrequent and appear to be reasonably well managed with symptomatic treatment alone. Because there is some concern about possible long-term neurobehavioral effects of barbiturate use during pregnancy, one might suggest the substitution of a narcotic in combination with acetaminophen for a medication containing a baributrate.[16] Even so, our patient's infrequent use of the medications renders this a minor point. Narcotics have many drawbacks when used for the acute treatment of migraine (egs, sedation, aggravation of nausea, abuse potential), but they do have a reassuring safety record in pregnancy. For many patients, they thus represent a reasonable treatment option for the relatively short duration of a pregnancy. Triptan medications are not currently recommended for use in pregnancy, although multiple sources of informa-

tion (including a prospective sumatriptan pregnancy registry) are sufficient to exclude a major increase in teratogenic risk for this class of drugs.[17-19] Because it has been commercially available the longest, most of the evidence currently available applies to sumatriptan, and whether these results are generalizable to other triptans is unclear. Most experts feel that we currently lack sufficient evidence to make a positive recommendation for sumatriptan use during pregnancy, but the information is reassuring for patients concerned about an unintended exposure during early pregnancy.

Likewise, there is no compelling reason in this case to add prophylactic therapy. If prophylactic therapy were felt to be necessary, expert opinion and experience in other disease states suggests that the medication with the best balance of safety and efficacy would be a low dose of a tricyclic antidepressant such as amitriptyline.[12] If anything, this case report suggests that it is the aura rather than the headache that is of more concern to the patient. Although furosemide and ketamine, as well as some other medications, have been anecdotally reported as helpful in treating aura, these options have limited practical potential and are primarily of interest because of what they suggest about the underlying pathophysiology of aura.[20,21]

In summary, the changes in headache and aura this patient is experiencing are not inconsistent with the course of migraine with aura during pregnancy. She can be reassured that no evidence exists to suggest that babies born to migraineurs are at increased risk of birth defects.[22] Her headache status and medication use will require frequent monitoring during the remainder of her pregnancy, and, if resources permit, she should be offered biofeedback and relaxation training.

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