ABSTRACT

Migraine affects 25% of the female population during childbearing years (aged 18–49 years). Managing chronic headache during pregnancy poses many challenges for the pregnant patient, her family, and treating clinicians. Although for many women, higher estrogen levels during pregnancy may result in less frequent or less severe headache episodes, for others headache may not improve, and may indeed worsen, particularly in the first trimester. There are few trials and little evidence-based data for many medications during pregnancy because of the obvious risks inherent in exposing the fetus to these drugs. This article will address what is currently known about the clinical and pathophysiologic evidence for headaches (predominantly migraine) associated with pregnancy, the epidemiology of the condition, in addition to the pharmacologic and nonpharmacologic treatment options available. The relative risks and recommendations for the most common pharmacologic therapies prescribed for acute and preventive treatment of headache will be discussed within the context of conception, pregnancy, and lactation.

ESTROGEN INFLUENCE ON PREGNANCY

As we know from the behavior of migraine throughout a woman’s reproductive cycle, hormone fluctuations correlate with migraine incidence, and this phenomenon holds true during pregnancy. Estrogen levels increase steadily throughout the first trimester, stabilize during the second and third trimester, and then sharply decline at postpartum. In one prospective study by Sances et al, 49 patients with migraine (2 with aura and 47 without aura) were followed during their pregnancies and 1 month postpartum to ascertain the course of their migraines. Migraine improved in 47% of the 47 patients who had migraine without aura during the first trimester, in 83% during the second trimester, and in 87% during the third trimester, whereas 11%, 53%, and 79% of the women, respectively, achieved complete remission. Migraine recurred during the first week after...
childbirth in 34% of the women and during the first month in 55%. The authors identified certain risk factors for the lack of improvement in migraine during pregnancy. The presence of menstrually related migraine before pregnancy was associated with a lack of headache improvement in the first and third trimesters, whereas second-trimester hyperemesis and a pathological pregnancy course were associated with a lack of headache improvement in the second trimester. Breastfeeding seemed to protect from migraine recurrence during the postpartum period. Although de novo migraine is rare (<3%), it typically occurs in the first trimester; likewise, permanent remission of migraine following pregnancy is also rare, with 94% of women reporting a return of migraine postpartum. Bottle feeding and age of 30 years or younger accelerate the return of migraines for these women.

**Epidemiology of Headache During Pregnancy**

The epidemiologic data for headache during pregnancy are limited, in that they are based largely on small studies following women over relatively short periods of time and not generally through multiple pregnancies. Migraine affects 25% of the female population during childbearing years (aged 18–49 years), although 50% to 80% of women report migraine improvement during pregnancy and 30% of women with tension-type headache (TTH) also improve—typically in the first trimester. One study by Scharff et al of 30 women followed prospectively throughout their pregnancies and for 12 weeks postpartum noted a nonsignificant decline throughout pregnancy, followed by a rise in migraine, TTH, and combined headache postpartum (during the birth week). According to the authors, in this study, unlike previous retrospective studies, patients with migraine demonstrated an increase in headache in the third trimester. In addition, parity seemed to play a role; there was a tendency in multiparous women for headaches to increase in the third trimester, whereas primiparous women reported less headache activity.

According to data from Wainscott et al, the risk of birth defects in the general population is 3% to 5%, whereas the prevalence of birth defects reported for patients with migraine was similar at 3.4%. Aube determined that migraine headaches did not appear to impact fertility rates. There were also no increased incidences of toxemia, abnormal labor, miscarriage, congenital malformations, or stillbirths reported in their study comparing 777 patients with migraine versus 182 control subjects without migraine. With regard to the natural history of their headaches, the authors noted that study participants experienced a 60% to 70% improvement in the frequency of migraines, particularly in the second and third trimesters, with 4% to 8% of women experiencing worsening of symptoms, and approximately 10% of migraine cases beginning during pregnancy. Prepregnancy headache patterns returned almost immediately postpartum.

**Management Strategies During Pregnancy**

For patients with episodic migraine (EM) who are already receiving effective treatment, it is important to provide education regarding the risk factors for conversion from EM to chronic migraine (CM). As they near the time that they want to achieve pregnancy, many women choose to taper and discontinue daily preventive medications to conceive while on no medications, thus beginning their pregnancy hoping migraine frequency will diminish and not require pharmacologic intervention. These patients can take measures to minimize any risk factors for progression or transformation to a chronic headache state and can tailor their therapies both pre- and postconception to minimize any potential risk to the fetus. In this regard, it is important to caution patients under treatment about the dangers of medication overuse.

Potential mothers who suffer from chronic daily headache (CDH) or CM may be encouraged to reduce their attacks to episodic status before they try to achieve pregnancy. Certainly, the decision to become pregnant is a major decision in a woman’s life, and one over which she should have as much control as possible. Therefore, the suggestion to delay pregnancy, pending stabilization of her headaches, must be conveyed in a compassionate, yet knowledgeable, environment emphasizing the benefit of optimizing headache management before achieving pregnancy.

It is important to confirm the diagnosis of migraine with aura for the pregnant woman, especially if she is experiencing her first migraine with aura. A complete diagnostic workup is indicated, including an evaluation for hypercoagulable states and appropriate imaging studies to assure the accuracy of her headache diagnosis and to rule out secondary causes. Once the
diagnosis is confirmed, an open, honest discussion about treatment options and medication risk is essential. In addition, aggressive, nonpharmacologic therapy is important.

For women with severe or frequent headaches who are considering pregnancy or who already have conceived, preventive therapy can be offered on the basis of comorbidities, how disabled the woman is from the headache, and responsiveness to acute therapy. These patients need to be followed frequently in the first and last stages of pregnancy—approximately every 2 to 4 weeks. Pregnant women with chronic headaches frequently find themselves in a situation of not being offered treatment because they are advised that their symptoms will improve or clinicians are reluctant to use medications during pregnancy. However, clinicians should offer safe and effective therapeutic regimens in the event of an exacerbation or transition to a chronic headache state. Throughout the pregnancy, women should be encouraged to monitor their headache histories and be asked about them at these visits. Do their headache patterns fluctuate? Are they developing chronic headache? Clinicians may then take these historical patterns into consideration when determining various treatment options (Sidebar 1).

TREATMENT OPTIONS

Because approximately 50% of pregnancies are unplanned, early inadvertent fetal exposure to medications is likely. Furthermore, according to data on file from an international survey conducted by the World Health Organization, 86% of 14 778 pregnant women surveyed took an average of 2.9 prescription medications during their pregnancies.10 Because medication use can be harmful early in pregnancy, management of chronic headache in young women must include evaluation of reproductive status and contraceptive use.

A prospective study by Marcus et al followed 49 women from early pregnancy to 3 months postpartum, noting headache improvement for only 41% of patients who reported a 30% improvement in their symptoms between the second and third trimester, which was not significant.3 The authors found that, if headache persisted through first trimester, it usually persisted through the remainder of pregnancy, and in those cases, cautious treatment should be instituted, with due consideration of risks.3

Failure to manage chronic headache in pregnancy may lead to poor nutrition, dehydration, depressive symptoms, exacerbation of comorbid disorders (ie, epilepsy or hypertension), and addiction (maternal/fetal) if the patient is offered opiates.11 Poor nutritional status and dehydration may predispose pregnant women to sinus thrombosis and hyperemesis gravidum.

The Figure illustrates treatment options for women with CDH to help them manage the transition between anticipating conception, conception, pregnancy, and lactation, if they choose to breastfeed. Pre-conception, women with chronic headache who are taking prophylaxis may be offered pharmacotherapy considered to be safe in pregnancy. Options include adding magnesium and vitamin B2. Other nonpharmacologic techniques may incorporate the use of massage, local ice or heat, and/or biofeedback. Folic acid supplementation, although not influencing headache, should be included for prevention of neural tube defects. As with any patient with headache, knowledge of headache triggers and avoidance of these is important.

For women who are already pregnant, pharmacologic treatment is determined by headache frequency and severity. The patient with infrequent migraine, (<2 headache-days/week) may discontinue any triptan she may be taking and rely on other conventional, acute medications, such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAID) up to 32 weeks, opiates, antiemetics, and corticosteroids. The discontinuation of triptans is controversial, given limited data from pregnancy registries.

For women who have frequent headache episodes (≥3 days/week), more severe attacks may be managed acutely; however, preventive medications also may be considered, using a prophylactic regimen that minimizes exposure to the fetus by using US Food and

### Sidebar 1. Management of the Woman with Headache

- Confirm headache diagnosis.
- Pursue aggressive nonpharmacologic treatments.
- Tailor pre- and postconception acute therapy to patient needs.
- Caution about medication overuse.
- Offer preventive therapies based on comorbidities, disability, and responsiveness to acute therapy.
- Adjust therapy on a monthly basis.
- Engage in open, honest discussions about risks.
Drug Administration (FDA) Class C (or above) medications (Table12; eg, β blockers, gabapentin, and topiramate). β-adrenergic blockers, such as propranolol, have demonstrated relative safety during pregnancy and are generally considered to be first-line preventive therapeutic agents; however, these medications should be tapered within the last weeks of pregnancy (typically at 36 weeks) to avoid maternal bradycardia or difficulty with labor.

Calcium channel blockers have been associated with fetal bradycardia and intrauterine growth retardation, and thus may not be prudent choices for preventive therapy.13,14 Tricyclic antidepressants (TCA), such as amitriptyline, have a long history of use in pregnancy, despite classification as pregnancy category D. Among the antiepileptic drugs (AED), gabapentin may be used while the patient is trying to conceive and during early pregnancy, but may be discontinued because of concerns related to delayed fetal bony growth plate development.15 Valproate is avoided in early pregnancy because of concerns about neural tube defects.16 Although topiramate has been associated with genital abnormalities, the number of affected patients has been relatively small.17 Medication overuse headache and its contribution to CDH is an important area in which to educate pregnant patients and to encourage nonpharmacologic therapies. Adequate rest and hydration, exercise, and proper nutrition to maintain optimal pregnancy weight (increased body metabolic index is associated with increased risk of CDH) should be emphasized.18

In terms of specific risks associated with acute medications, studies have linked NSAIDs to inhibition of implantation in early pregnancy19,20 and with premature closure of fetal ductus arteriosus in later pregnancy.21,22 To avoid the possibility of patent ductus arteriosus, it is prudent to discontinue NSAID use before week 32.23

One of the oldest opioids in use for headache during pregnancy is codeine. The greatest risk associated with this medication is development of cleft palate or other midline malformations. In addition, use in the later stages of pregnancy may result in delivery of an infant addicted to opiates. The use of triptans during pregnancy remains controversial. Although the triptans are considered to be pregnancy category C, these medications are typically reserved for specific populations of women as a second- or third-line of therapy. Sumatriptan has the largest pregnancy registry because it was the first triptan introduced in the United States, and as of 2005, there has been no evidence of structural malformations among 438 women listed in this registry; its Teratogen Information System (TERIS) rating is “undetermined” (Sidebar 2).24

CDH = chronic daily headache; HA = headache; NSAID = nonsteroidal anti-inflammatory drug; TCA = tricyclic antidepressants.

### Table. US FDA Classification of Drugs Used in Pregnancy

<table>
<thead>
<tr>
<th>Category</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled human studies show no risk.</td>
</tr>
<tr>
<td>B</td>
<td>Controlled studies show no evidence of risk in humans, despite adverse findings in animals. Chance of fetal harm is remote but remains a possibility.</td>
</tr>
<tr>
<td>C</td>
<td>Risk to humans cannot be ruled out. Adequate well-controlled human studies are lacking, and animal studies have shown risk to the fetus or are lacking.</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of risk to humans from human studies or postmarketing data.</td>
</tr>
<tr>
<td>X</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

FDA = Food and Drug Administration. Data from Physician’s Desk Reference.21
Finally, among the acute medications, use of corticosteroids may improve lung function and lung maturation for fetuses carried by women who may be experiencing preterm labor. However, recently, there have been concerns about pituitary dysfunction in these infants typically related to chronic steroid use; this concern may not be applicable to women intermittently using steroids only for acute headache attacks.

**Issues During the Postpartum State**

Headache is a common postpartum complaint, affecting 39% of all women, and 50% of all patients with migraine. Nearly all women (94%) reported the return of migraines after delivery. Factors accelerating the return of migraine postpartum include bottle feeding and age of 30 years or younger. The incidence of migraine is reported to be low during breastfeeding; however, for some women, lactation is unlikely to alter headache.

Some drugs bind strongly to proteins in milk, and in the past, breastfeeding women were advised to pump and discard breast milk to avoid transmission to infants. More recently, sumatriptan has been approved by the American Academy of Pediatrics for use during breastfeeding. Other safe choices for acute headache treatment during lactation include prochlorperazine, ondansetron, and acetaminophen.

**Classification System for Medications Used During Pregnancy and Lactation**

The most commonly used system for classifying drugs according to their teratogenicity is the US FDA rating system; however, other systems are also in use. For example, the TERIS rating scale is designed to assess teratogenic risk of drug exposure to the fetus. The rating is based on expert opinion and existing medical literature and does not necessarily correlate with the US FDA pregnancy rating (Sidebar 2).

The Table lists the US FDA rating system for safe use of drugs during pregnancy. Among the preventive medications, most are US FDA category C or D. Category C medications include β blockers, calcium channel blockers, topiramate, gabapentin, selective serotonin reuptake inhibitors, and doxepin. Other antidepressants, including amitriptyline and nortriptyline, in addition to the AED, divalproex sodium, are pregnancy category D. Ergotamine, phentotoin, valproic acid, and lithium carbonate are all contraindicated in pregnancy (pregnancy category X). Animal data for ergots suggest that these drugs can inhibit implantation of the embryo and result in cleft palate and bilateral limb defects. Human data indicate that ergots also have an abortifacient action. The teratogenic effects for these drugs are unknown.

Acetaminophen is US FDA category B and has “no evidence of teratogenicity” per its TERIS rating. However, acetaminophen may have transient adverse effects on the uterus and on platelet function. Caffeine, another common ingredient in over-the-counter and prescription headache remedies, is US FDA category C, whereas meperidine, methadone, and morphine are category B. All have a Briggs Rating of category D during the third trimester. There is the possibility of maternal and fetal
dependence, and codeine may be associated with cleft lip, cleft palate, inguinal hernia, hip dislocation, and cardiac/respiratory defects. Likewise, butalbital is Briggs category C/D in the third trimester. Although there is no known risk of abnormalities, it can cause fetal dependence and withdrawal from prolonged use. Selected neuroleptics and antiemetics are classified as US FDA category C (eg, chlorpromazine, haloperidol, and prochlorperazine) whereas metoclopramide and ondansetron are US FDA category B. Steroid molecules are large and do not generally cross the placenta. Therefore, prednisone is US FDA category B and dexamethasone is category C. There have been no confirmed reports of congenital malformations.

CONCLUSIONS

Clear focused and evidence-based treatment algorithms are needed for management of headache during conception, pregnancy, and the postpartum period. Although most studies seem to indicate that headaches improve for most women during pregnancy as estrogen levels increase, this appears often not the case in women with more severe, frequent migraine. Pharmacologic studies are limited in pregnant women for obvious reasons; thus, evidence-based treatments are lacking. Pregnancy registries to record adverse outcomes for various medications and large, population-based studies are needed to analyze the behavior of chronic headache, particularly CM, during pregnancy. Collaboration between headache specialists and obstetricians is needed to promote research and education for the optimal management of headache during pregnancy.

DISCUSSION

Dr Robbins: I would like to make a couple of points regarding the need to overhaul the TERIS and US FDA ratings. The TERIS is acceptable in terms of looking at exposure, and then what happens later on; however, the US FDA rating is based more on animal studies. For instance, bupropion was just reclassified as a pregnancy category C based on a small rat study. We need better prospective studies, such as the studies being done for anticonvulsant drugs. In one such study conducted in England and Europe, valproate, topiramate, and phenytoin had adverse effects, with phenytoin having the most. Lamotrigine, which has had a prospective study going on since 1992, has an adverse event rate of 3%, which is well within accepted parameters; however, it may not be the best choice for headaches in terms of efficacy. Carbamazepine is always very low in terms of side effects at 2%, and oxcarbazepine seems to have a similar low rate of adverse events, which has demonstrated decent efficacy in off-label use for some patients with CDH.

Dr Brandes: I think we can reassure patients with migraine that we have more data for the AEDs that are also used in migraine because those women who are pregnant typically do not have a choice about coming off their AED and are often included in larger, randomized, double-blind, placebo-controlled trials.

Dr Robbins: The more critical problem with the anticonvulsants is not fetal effects, but rather neurobehavioral problems and IQ changes 10 years later. For example, phenytoin has marked effects—a later reduction of 10 points on IQ scores. Among the antidepressant drugs, not all of the TCAs are category D. Protriptyline is category C. If you look at the TERIS system, they list these medications as “none to minimal,” which is better for amitriptyline than the US FDA category D rating.

Dr Brandes: There is not any current methodology for including the historical data—the fact that we have had amitriptyline in use for approximately 60 years. One would think that that also could be incorporated into the ratings, but unfortunately it is not. You could argue that there is a certain amount of intuition and a certain amount of judgment that goes into analysis of risks and benefits for each drug, and rating differences are sometimes subtle.

Dr Ramadan: Do you know what obstetricians think about continuing or initiating the cyclooxygenase (COX)-2 inhibitor medications in these patients, particularly in patients who have comorbidity with arthritic conditions?

Dr Brandes: In my region, patients are not allowed to continue to use these drugs during pregnancy; they are treated essentially like the standard NSAIDs. Some of the obstetricians, in the first 6 to 8 weeks after conception—which corresponds approximately to weeks 4 to 6 up through weeks 12 to 18—will allow COX-2 inhibitors, but only for occasional, not daily, use. Although it is not a large patient population, women with rheumatoid arthritis or with mixed connective tissue disorders sometimes do remain on prednisone throughout their pregnancies.

Dr Mondell: Are there any comments about botulinum toxin in this setting?
Dr Brandes: There have been a few anecdotal reports of botulinum toxin use during pregnancy. Miscarriage has been reported in association with botulinum toxin, and yet, there was also a report of a woman who received botulinum toxin throughout 3 pregnancies and had normal, healthy infants. I think it falls into the category where we just do not have enough information. The drug has been used in breastfeeding mothers without adverse event, but the numbers are small. I would be hesitant to advocate its use.

Dr Mondell: What about being proactive, meaning before pregnancy being anticipated, using botulinum toxin?

Dr Brandes: I think that because of the lack of data, I would not use it, but you could argue both ways. On the positive side, if a woman benefited from the drug, she would have benefit for approximately 12 to 16 weeks, but the difficulty would be that you would have committed the patient to continued exposure to the drug in the first trimester. The one thing about some of the other agents is that, even if patients become pregnant on a drug, you have the luxury of stopping them, and within a matter of days, most agents are out of their system.

Dr Medina: Quite a significant proportion of patients will tell you that, “The best treatment I’ve ever had for migraine frequency is to get pregnant.” Those who do very well during pregnancy, in my experience, quite often do very badly during the postpartum period. You commented on nursing as delaying the deterioration of the migraine. I wonder if you ever thought about what the mechanism of that might be.

Dr Brandes: I do not know the answer in terms of mechanism. What I see fairly consistently is that prolonged lactation tends to worsen migraine. I am always very challenged with the woman who comes to see me who has not perhaps had CDH during her pregnancy or CM but has had EM, and she is now into her 20th month of breastfeeding. I have had patients who have breastfed their children for 4 years. I think it would be interesting to map prolactin levels for that prolonged period of time. The other issue in breastfeeding, which is not addressed in many of the studies, is the interruption in terms of sleep, and what that may do physiologically. In terms of nonpharmacologic treatment strategies, we try to get the woman to pump late in the evening and let her husband or partner feed the baby with the breast milk if she does not want to give it up. It would be helpful if we could begin to collect that prolonged breast-feeding data.

Dr Ramadan: There are data about prolactin, estrogens, and other hormones. In terms of lactation, there are actually quite a bit of animal data on synaptic modulation and synaptogenesis with oxytocin, but relationship is unknown, but that certainly would be a fascinating area to explore.

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