SECTION VII

Special Problems in the Headaches and Their Management

Chapter 133

Headaches During Pregnancy and Lactation

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EVALUATION OF HEADACHE IN PREGNANCY

In the case of a pre-existing primary headache disorder, headaches occurring during pregnancy do not generally pose a diagnostic problem. However, new-onset headaches that do not satisfy diagnostic criteria for a benign headache disorder or pre-existing headaches that undergo an ominous change in pattern in a pregnant patient may require evaluation. In general, this evaluation should be as comprehensive as that in a nonpregnant patient, including appropriate imaging studies if necessary.

Risks of Neuroimaging During Pregnancy

A standard head or cervical spine computed tomography (CT) scan exposes the uterus to less than 0.1 mGy of radiation. This is well below the threshold dose for fetal anomalies, which is estimated to be 10 to 50 mGy. The use of iodine contrast agents is possible if necessary, but may increase the risk of hypothyroidism when used after the second trimester (36). Magnetic resonance imaging and angiography appear to be safe in pregnancy. Four studies (two in animals, two in humans) have suggested no increased risk of adverse reproductive outcome associated with in utero exposure to this technology. One study suggested a twofold increased incidence of eye malformations. Low–molecular-weight contrast agents do cross the placental barrier, but a single dose of 0.1 to 0.3 mmol/kg probably imposes an extremely low risk of fetal injury. Nonetheless, it is advisable to avoid the use of contrast where possible (8).

PHARMACOLOGIC TREATMENT OF HEADACHE DURING PREGNANCY

Prescription drug use is common during pregnancy. A World Health Organization survey showed that 86% of pregnant women used prescription medications, with an average of 2.9 prescriptions per woman (6). In a survey of pregnant women at Parkland Memorial Hospital in Dallas, 40% took some type of medication other than iron or vitamin supplements, and up to 20% used an illicit drug or alcohol (25).

Until late in the last century, fetal drug exposure during pregnancy was viewed with relative complacency. A prevalent belief was that the placenta acted to shield the developing fetus from harmful effects of maternally ingested substances (3). This relaxed attitude is in stark contrast to current views, in which there is deep, sometimes unwarranted, suspicion of any drug as a potential cause of serious birth defects. Chief among the factors leading to this dramatic change in philosophy was the thalidomide tragedy of the 1960s. The occurrence of limb and other birth defects in children born to mothers who had taken thalidomide during pregnancy heightened public and professional awareness of potential negative drug effects on a developing fetus (23). Since then, other drugs with teratogenic effects have been identified, including diethylstilbestrol (DES), isotretinoin (Retin-A), and valproic acid. Although fewer than 30 drugs have been proven to be human

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teratogens at clinically relevant doses, public and professional concern about the risks associated with prenatal drug exposure continues to be high.

This attitude of caution has led to disclaimers on marketed products that discourage drug use in pregnancy "unless the potential benefits justify the potential risks to the fetus." Such statements likely contribute to the common perception among pregnant women that drugs that have not been proven safe in pregnancy are therefore dangerous. There is evidence that, at least in some cases, anxiety resulting from inaccurate estimates of risk has caused women to seek induced abortion after inadvertent drug exposure during pregnancy (22). Incorrect assumptions about the risk of certain drugs may also contribute to withholding of medically indicated treatment during pregnancy and has led to the withdrawal of effective, useful, and safe drugs from the marketplace.

HOW HEADACHE DRUGS CAN AFFECT PREGNANCY

Teratogenesis

Teratogens lead to dysgenesis of a specific fetal organ system that results in functional or structural abnormalities. The abnormalities caused may vary in severity from relatively minor effects (malformed ears or hypospadias, for example) to life-threatening problems (renal agenesis). Drug exposure during the first trimester of pregnancy is of particular concern, since most organ formation occurs during this time (33). Unfortunately, many women may not be aware of pregnancy until much of this critical time has passed.

Drugs that are teratogens do not have random, nonspecific effects on the developing fetus. Rather, a particular drug leads to a characteristic pattern of malformations. For a defect to result, exposure to the teratogen must occur at the time that the organ system in question is forming; exposure before or after this period will not result in teratogenesis. In addition, exposure to a teratogenic drug during the first 2 weeks of pregnancy, when fetal cells are undifferentiated, usually results in an "all or nothing" effect in which the fetus is either destroyed or emerges unaffected. Only a portion of fetuses exposed during the critical period of organ formation will develop a defect; this likely reflects varying degrees of genetic vulnerability as well as critical exposure levels that may not always be reached. In addition, some compounds may be only weak teratogens; the resulting very low rates of malformations will be difficult, if not impossible, to detect even with careful surveillance. Thalidomide, for example, causes birth defects in 20 to 30% of exposed pregnancies, whereas valproic acid causes neural tube defects in 1 to 2% of exposed pregnancies (17).

Valproic acid is the headache drug for which there is the strongest and most concerning evidence of teratogenesis, in the form of neural tube defects. However, at least some neural tube defects might be prevented by folate supplementation, since a woman's risk of having a child with a neural tube defect is associated with early pregnancy red cell folate levels in a continuous dose–response relationship (11). Valproic acid does not produce folate deficiency, but it may interfere with the production of folinic acid by inhibiting glutamate formyl transferase (42). Barbiturates can also impair folate absorption. Thus, advice to all headache patients of childbearing potential should include recommendations to obtain at least 1 to 2 mg of folate, a level of intake that generally requires the use of folate supplements (10).

Long-Term Developmental Effects

In addition to teratogenic effects resulting in recognizable structural or functional alterations in organ systems, more subtle functional, cognitive, or neurobehavioral changes can occur as a result of drug exposure during pregnancy. These are obviously much more difficult to detect; costly and complex long-term follow-up studies are required to establish a cause-and-effect relationship. Barbiturates, an ingredient in commonly used headache medications in the United States and Canada, are suspected of causing long-term neurobehavioral effects.

Other Effects on Pregnancy

Drugs used for headache can have myriad other effects on pregnancy, including lengthening labor (magnesium and verapamil) (16), affecting fetal birth weight (beta-adrenergic blockers) (24), or causing other physiologic effects. Some of these effects may be specific to the stage of pregnancy in which the drug is taken. Drugs that interfere with prostaglandin formation, such as aspirin, can cause premature closure of the ductus arteriosus if taken late in pregnancy, while they are generally without adverse effects if taken early in pregnancy (23). Other drugs emerging for use in migraine may have serious adverse effects during pregnancy. For example, preliminary information suggests that lisinopril is an effective migraine preventive agent (35). However, angiotensin-converting enzyme inhibitor use during pregnancy, especially in the second and third trimesters, can cause low blood pressure, severe kidney failure, potassium excess, or even death in the newborn. Studies in mice and rats at doses many times the recommended human dose have shown that use of lisinopril causes a decrease in successful pregnancies, a decrease in the weight of infants, and an increase in infant deaths (18).

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THE EFFECTS OF MIGRAINE ON PREGNANCY OUTCOME

The effects of drugs used to treat migraine or other headache disorders must also be separated from the effects of the disease the drug is intended to treat. There is limited information about whether women with migraine are at higher risk of delivering infants with birth defects or other adverse pregnancy outcomes. One study of pregnancy outcome in 450 migraineurs compared with 136 nonmigrainous controls found no increased risk of poor pregnancy outcomes (40). Evidence from a Danish study suggested a possible increased risk for low birth weight (less than 2500 g), but the sample size was small (30).

MANAGEMENT OF HEADACHE IN PREGNANCY

In general, the same treatments that are helpful in nonpregnant patients are used, with exceptions for drugs that are known or suspected of having harmful effects in pregnancy. Treatment needs to be varied among patients. Women with occasional, moderate attacks of headache are often very motivated to avoid or minimize drug use, but women with frequent, disabling attacks of migraine or those who experience severe nausea and vomiting leading to dehydration usually require pharmacologic treatment. Those complications pose a risk to the fetus that is probably greater than the potential risk of the medications used to treat the pregnant patient (38).

MIGRAINE TREATMENT

Abortive Therapy—Overview

Abortive, or symptomatic, treatment is meant to reduce the severity and duration of symptoms in an acute headache attack. Initial attempts to treat mild or moderate attacks should emphasize rest, ice, relaxation strategies, and other nonpharmacologic methods of treatment. For headaches that do not respond to nonpharmacologic treatment, symptomatic drugs are indicated. Severe acute attacks of migraine should be treated aggressively. Drugs with a longer record of use in pain treatment, such as nonspecific opioid analgesics, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs), or sedating phenothiazines are generally preferred. In the pregnant patient, this includes the use of intravenous hydration and a sedating antiemetic, for example prochlorperazine 10 mg intravenously. Intravenous opioids or corticosteroids are also useful. In France, infusions of amitriptyline are used except during the third trimester.

The associated symptoms of migraine, such as nausea and vomiting, can be as disabling as the headache pain itself. Metoclopramide, which decreases the gastric atony seen with migraine and enhances the absorption of coadministered medications, is especially useful in migraine treatment (39). Mild nausea can be treated with phosphorylated carbohydrate solution (Emetrol) or doxylamine succinate and vitamin B6 (pyridoxine) (23). More severe nausea may require the use of injections or suppositories. Trimethobenzamide, chlorpromazine, prochlorperazine, and promethazine are available orally, parenterally, and by suppository and can all be used safely.

NSAIDs, acetaminophen (alone or with an opioid), or opioids alone can be used during pregnancy (23). Aspirin in low intermittent doses is not a significant teratogenic risk, although large doses, especially if given near term, may be associated with maternal and fetal bleeding. Aspirin should probably be avoided unless there is a definite therapeutic need for it (other than headache). In general, NSAIDs may be taken safely for pain during the first trimester of pregnancy. However, their use should be limited during later pregnancy because some NSAIDs may constrict or close the fetal ductus arteriosus (23). Other authors believe that the most potent inhibitors of prostaglandin synthesis, such as salicylates and indomethacin, should be avoided throughout pregnancy if possible, and certainly during the last trimester (7). Barbiturate and benzodiazepine use should be limited.

Pregnancy Risks Associated With Migraine-Specific Medications

As of January 2004, information from the prospective sumatriptan pregnancy registry showed no statistically significant difference between the rate of birth defects in pregnancies where first-trimester exposure to sumatriptan occurred and the background rate of birth defects in the general population (1). Complementary sources of information about triptan risk in pregnancy include the Swedish Medical Birth Registry (21), the Danish Birth Registry (31), a Canadian teratogen information service study (37), and a year-long postsurveillance safety study during which unintended pregnancies occurring during sumatriptan use were prospectively followed (32). These sources of information have likewise produced no signal of teratogenicity from triptan use. No single method of assessing drug risk in pregnancy provides complete or perfect information, but the consistency of information from multiple sources of data is reassuring information for the woman whose fetus has been inadvertently exposed to sumatriptan during pregnancy (26).

The limitations of current information must be appreciated, however. A large increase in risk for a single birth defect from sumatriptan exposure can be confidently

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excluded based on present information, but a small increase in risk for common birth defects or a modest increase in risk for rare birth defects cannot be ruled out, based on the number of pregnancy outcomes for which we have information. This is because if a drug is associated with a high level of birth defects (e.g., thalidomide), relatively few exposures are needed to detect this risk; if the medication is associated with a slight increase in the overall occurrence of birth defects, approximately 300 exposed pregnancies need to be followed to detect a doubling of risk; and if the medication is associated with a rare increase of a specific defect (e.g., 1 in 1000), approximately 10,000 exposed pregnancies need to be followed to detect a doubling of risk (26).

In the authors' view, the current classification of triptans as Pregnancy Category C in the widely used United States Food and Drug Administration (FDA) Pregnancy Classification remains appropriate. For drugs in Category C, "safety in human pregnancy has not been determined" and "...potential benefits should justify potential risks" if used in pregnancy. Thus, in deciding whether to recommend the use of sumatriptan in pregnancy, the risks of the drug must be weighed against the beneficial effects of treatment. The FDA's five categories of pregnancy risk (A, B, C, D, and X) are intended to assess the therapeutic risks of drugs, and emphasize weighing treatment benefits against drawbacks (Table 133-1) (29). The system has been widely criticized. For example, tricyclic antidepressants are still classified as class D, even though the evidence suggests they are safe (23). An alternative method of assessing drug risks in pregnancy is the TERIS system (Teratogen Information System), a computerized database of information "designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women." TERIS ratings classify a drug risk as "none," "minimal," "small," "moderate," "high," or "undetermined." Within the TERIS system, decisions about risk are made "on the basis of the reproducibility, consistency, and biological plausibility of available clinical, epidemiological, and experimental data." Information on over 1000 drugs is available in this system, although access to the information requires a subscription (19). The TERIS rating for an individual drug is based on a consensus of expert opinion and the literature (14). There is limited agreement between TERIS and FDA ratings of risks (Table 133-2) (13).

TABLE 133-1 United States Food and Drug Administration Categories of Medication Risk in Pregnancy

Category A	Controlled human studies show no risk.
Category B	No evidence of risk in humans, but there are no controlled human studies
Category C	Risk to humans has not been ruled out
Category D	Positive evidence of risk to humans from human or animal studies
Category X	Contraindicated in pregnancy

TABLE 133-2 Teratogen Information Service (TERIS) Pregnancy Risk Ratings*

N	None (A)
N–Min	None–minimal (A)
Min	Minimal (B)
Min–S	Minimal–small (D)
S	Small
S–Mod	Small–moderate
Mod	Moderate
H	High (X)
U	Undetermined (C)

*Equivalent U.S. Food and Drug Administration ratings in parentheses, where applicable.

Ergotamine, a nonselective serotonin agonist, is generally considered contraindicated in pregnancy based on evidence suggesting it increases prenatal mortality, may be linked to fetal hypoxia and growth retardation, and produces pronounced effects on blood flow to the placenta, as well as an increase in uterine muscle tone (15,20). In contrast, sumatriptan does not appear to increase uterine contractions in animal studies (12). The risk of other migraine drugs during pregnancy is speculative, because controlled studies or other comprehensive sources of information are lacking. According to the Perinatal Collaborative Project, a prospective and concurrent epidemiologic study of more than 50,000 pregnancies, many drugs have little or no human teratogenic risk (4). Table 133-3 summarizes U.S. FDA, TERIS, and American Academy of Pediatrics (AAP) recommendations about the use of specific migraine medications during pregnancy and lactation.

Preventive Treatment

Preventive therapy is designed to reduce the frequency and severity of headache attacks. In nonpregnant patients, preventive therapy is often recommended at a headache frequency of two attacks per month; in the pregnant patient, the threshold for treatment is generally higher. Patients whose headaches cannot be adequately managed with abortive therapy alone or who are at risk of other complications from unrelieved headache are the best candidates. If possible, treatment should be delayed until the second trimester or later, because the risk of adverse effects is probably less once major organ systems have formed. Beta-adrenergic blockers are preferred agents (27). The patient and her partner should be informed of the potential for adverse pregnancy outcomes that are known and should understand that in many cases information about safe use in pregnancy is lacking.

Nonpharmacologic therapy can be as effective as medication treatment for the prevention of many forms of

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TABLE 133-3 FDA, TERIS, and AAP Ratings of Some Commonly Used Nonspecific Headache Medications

	FDA	*TERIS*	*Lactation (AAP)*
Simple analgesics			
Aspirin	C[a]	N–Min	Caution
Acetaminophen	B	N	Compatible
Caffeine	B	N–Min	Compatible
NSAIDs			
Fenoprofen	B[a]	U	Compatible
Ibuprofen	B[a]	N–Min	Compatible
Indomethacin	B[a]	N	Compatible
Ketorolac	B[a]	U	Caution
Meclofenamate	B[a]	U	Compatible
Naproxen	B[a]	U	Compatible
Sulindac	B[a]	U	Compatible
Tolmectin	B[a]	U	Compatible
Narcotics			
Butorphanol	B[b]	N–Min	Compatible
Codeine	C[b]	N–Min	Compatible
Hydromorphone	B[b]	N–Min	Compatible
Meperidine	B[b]	N–Min	Compatible
Methadone	B[b]	N–Min	Compatible
Morphine	B[b]	N–Min	Compatible
Propoxyphene	C[b]	N–Min	Compatible
Neuroleptics			
Phenothiazines			
Chlorpromazine	C	N–Min	Concern
Prochlorperazine	C	N	Compatible
Promethazine	C	N	NA
Promazine	C	U	NA
Butyrophenones			
Haloperidol	C	N–Min	Concern
Thioxanthenes			
Thiothixene	C	U	NA
Other			
Metoclopramide	B	N–Min	Concern
Antiemetics			
Emmetrol	B	U	Compatible
Doxylamine and vitamin B6	B	N	NA
Trimethobenzamide	C	N–Min	NA
Corticosteroids			
Cortisone	D	N–Min	Compatible
Dexamethasone	C	N–Min	Compatible
Prednisone	B	N–Min	Compatible
Antihistamines			
Cyclizine	B	U	NA
Cyproheptadine	B	U	Contraindicated
Dimenhydrinate	B	U	NA
Meclizine	B	N–Min	NA
Barbiturates			
Butalbital	C	N–Min	Caution
Phenobarbital	C	N–Min	Caution
Benzodiazapines			
Chlordiazepoxide	D	N–Min	Concern
Clonazepam	D	U	Concern
Diazepam	D	N–Min	Concern
Lorazepam	D	U	Concern
Other			
Zolpidem	B	U	Not recommended
Anticonvulsants			
Carbamazepine	C	S	Compatible
Gabapentin	C	U	Uncertain
Phenytoin	D	S-Mod	Compatible
Valproic acid	D	S-Mod	Compatible
Antidepressants			
Tricyclics			
Amitriptyline	D	N–Min	Concern
Doxepin	C	U	Concern
Nortriptyline	D	U	Concern
Protriptyline	C	U	Concern
SSRIs			
Fluoxetine	B	N	Caution
Paroxetine	C	U	Concern
Sertraline	B	U	Concern
Monoamine oxidase inhibitors			
Phenelzine	C	U	Concern
Antihypertensives			
Beta-blockers			
Atenolol	C	U	Compatible
Metoprolol	B	U	Compatible
Nadolol	C	U	Compatible
Propranolol	C	U	Compatible
Timolol	C	U	Compatible
Adrenergic blockers			
Clonidine	C	U	Compatible
Calcium channel blockers			
Verapamil	C	U	Compatible
Angiotensin-converting enzyme			
Inhibitors	X		Caution
Angiotensin receptor blockers			

[a]D if third trimester
[b]D if prolonged or at term
N, none; Min, minimal; U, uncertain; NA, not assessed.

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TABLE 133-4 FDA, TERIS, and AAP Ratings of Specific Headache Medications

	FDA	TERIS	Lactation (AAP)
Ergots			
Ergotamine	X	Min	Contraindicated
Dihydroergotamine	X	U	Contraindicated
Methylergonovine	C	U	Caution
Methysergide	D	U	Caution
Triptans			
Naratriptan	C	U	Effects unknown
Rizatriptan	C	U	Effects unknown
Sumatriptan	C	U	Compatible
Zolmitriptan	C	U	Effects unknown
Frovatriptan	C	U	Effects unknown
Eletriptan	C	U	Effects unknown
Almotriptan	C	U	Effects unknown

Min, minimal; U, uncertain.

primary headache. One study compared treatment with amitriptyline to a stress management program and found a superior reduction in the headache index in the group receiving stress management (9). The combination of thermal biofeedback and minimal therapist contact relaxation was effective in reducing headache by at least 50% in 79% of pregnant women with benign headache, and benefits persisted following delivery (28,34). Table 133-4 summarizes recommendations from the U.S. FDA, TERIS, and AAP regarding the use of some common headache preventive treatments in pregnancy and lactation.

LACTATION

Breastfeeding provides important health benefits for both mothers and babies, and should be encouraged. A large case series demonstrated no significant effects of lactation on headache activity in a large group of lactating migraineurs (41). Because there are many options for treatment of headache, women should not be made to feel that they must choose between adequate pain control and nursing. As in pregnant patients, nonpharmacologic strategies should be emphasized in lactating women with headache, but many women will still need to use medication, particularly for acute attacks of migraine.

The major concern in migraineurs using medication is the possible effect of medications on the infant through transmission of the medication in breast milk. The amount of a maternal medication dose that appears in breast milk varies depending on the lipid solubility of the drug and other pharmacokinetic factors. The frequency of nursing and the time elapsed between maternal ingestion of the drug and nursing probably also influence drug levels in milk (5). Timing doses immediately after breastfeeding has occurred or pumping and discarding milk following a dose (and substituting formula or previously expressed and stored breast milk for infant feedings) are options that may minimize a baby's drug exposure. For many drugs, the concentration in breast milk is only a small fraction of the maternal blood level; in fact, most drugs have little or no effect on milk supply or the baby although virtually all will be present in breast milk in small amounts.

The AAP Committee on Drugs makes recommendations about the compatibility of commonly used medications with breastfeeding. They categorize drugs as (a) contraindicated, (b) requires temporary cessation of breastfeeding, (c) effects unknown but may be of concern, (d) use with caution, and (e) usually compatible (2). The AAP has recently added sumatriptan to the list of drugs that are compatible with lactation; because sumatriptan is less lipophilic than other triptans, this recommendation cannot necessarily be extrapolated to other triptans. In five lactating women who received a 6-mg subcutaneous injection of sumatriptan, the peak breast milk concentration of the drug occurred at 2.6 hours (87.2 μg/L) and declined rapidly over 6 hours. When adjusted for weight, the infant dose was thus calculated to be only 0.5% of the oral maternal dose (43). AAP recommendations about the compatibility of some commonly used headache drugs with breastfeeding are contained in Table 133-3.

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