

Review Article

Headache in pregnancy: Recent insight.

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Background- In 1984, one of the first reviews of the role of estrogen in migraine noted that "the femaleness of the migraine condition is inescapable.¹ Headaches occur in over 80 percent of women during their childbearing years, thus they often present during pregnancy.^{2,3} The hormonal changes accompanying the menstrual cycle, pregnancy, and the postpartum period are thought to be responsible for many headaches in women of reproductive age.⁴ More than 90 percent of these headaches are either migraine or tension-type headaches,⁵ both of which are typically more severe in women than in men.⁶

Unfortunately, no large trials of headache therapy in pregnant women are available to provide data on which to base therapeutic recommendations. The major consideration is to "do no harm" since a history of headaches does not appear to adversely affect pregnancy outcome.⁷ Treatment decisions are made according to recommendations for nonpregnant adults with avoidance of drugs that are considered teratogenic or otherwise known to be harmful in pregnancy (eg, uterotonic agents, vasoconstrictors). Management of migraine in pregnant women is especially difficult because some anti-migraine medication is potentially teratogenic. Many drugs have been shown to cross the placental barrier, producing pharmacological or teratogenic effects in the fetus.

Migraine Headache - The prevalence of migraine headache is higher in women than in men and peaks during the childbearing years. Estradiol receptors are located in close proximity to 50 to 80 percent of catecholamine receptor sites in the brain, suggesting estrogen may affect the function of pain pathways.^{8,9}

Migraine headaches are associated with menarche, menstruation, oral contraceptive use, pregnancy, menopause, and postmenopausal hormone therapy, all of which are partially mediated by fluctuations in estrogen levels.¹⁰ In addition, supplementation with estrogen, but not progesterone, has been demonstrated to prevent menstrual (catamenial) migraines.^{11,12} Most women (48 to 79 percent) with migraine headaches report improvement during pregnancy.^{3,5,13-16} Remain unchanged in 5-30% cases.¹⁷ Although intensity of pain is subjective, 3.5 to 7 percent of patients report that their migraines are "worse" during pregnancy.¹⁵ Migraine headaches developing for the first time during pregnancy usually do so in the first trimester. One prospective longitudinal study found that recurrent migraine headaches primarily occurred in the third trimester, particularly in multiparous women,⁴ but most others have reported the prevalence of migraine is lowest in the third trimester.^{14,17} Recurrence during the postpartum period is common, but significantly less frequent in women who breastfeed.^{14,15,18}

A review of studies evaluating pregnancy outcome in migraineurs concluded that migraine headaches, treated or untreated, probably have no effect on pregnancy outcome (Miscarriage, stillbirths, congenital defects).^{19,20,21,22}

Treatment of migraine headaches - The treatment of migraine headaches in pregnant women differs from that in nonpregnant women because of concerns about the effects of certain drugs on the fetus (Table I). Non-drug therapy should be tried first. We suggest initiating therapy with acetaminophen (FDA pregnancy risk category B) and does not appear to increase the risk of adverse effects on pregnancy or the fetus.^{23,24} Women who do not respond after several days should be evaluated for provoking factors and treated more aggressively. This may include intravenous hydration, antiemetics, magnesium sulfate, and/or intravenous narcotics. Nonsteroidal antiinflammatory drugs (NSAIDs)(FDA pregnancy risk category B) are another option, especially in the second trimester. Their use should be limited to fewer than 48 hours in the third trimester due to concerns about premature ductal closure, platelet inhibition, and oligohydramnios. Opioids are a third-tier option, but should not be used on a chronic basis since they are habit-forming and can contribute to the development of medication overuse and chronic daily headaches.^{25,26} For moderate to severe symptoms, triptans may be considered. Selective serotonin agonists that are highly effective in treating migraine headaches. They selectively vasoconstrict

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brain vessels, but there is a theoretic possibility of vasoconstriction of uteroplacental vessels and increased uterotonic activity.²⁷ Human experience with sumatriptan exposure during pregnancy has been reassuring.²⁸ A significant number of patients will not respond to acetaminophen and will develop rebound headaches with use of narcotics. In these complicated cases, sumatriptan can be used to abort a migraine.²⁹ There is no definitive evidence of teratogenicity from sumatriptan.³⁰ Dopamine antagonists such as metoclopramide or phenothiazines such as prochlorperazine can be administered to relieve nausea and vomiting associated with migraine or migraine therapy. Neither drug is considered teratogenic.^{23,31}

Ergotamine is absolutely contraindicated (Table II) during pregnancy because of the potential to induce hypertonic uterine contractions and vasoconstriction, which could cause adverse fetal effects. Several non-pharmacological therapies including relaxation training, biofeedback, and physical therapy have been demonstrated to be effective in pregnant women.^{32,33} Should pharmacological therapy be necessary, all attempts should be made to avoid medications during the first trimester. If possible, pharmacological therapy other than acetaminophen and meperidine should be reserved only for women in the second and third trimesters who have frequent and severe attacks accompanied by vomiting and possible dehydration.

Table I: Analgesic in pregnancy³⁴

Drugs	First trimester	Second trimester	Third trimester
Acetaminophen	OK	OK	OK
Codeine	OK	OK	Avoid
Aspirin	(OK)	(OK)	Avoid
Diclofenac	(OK)	(OK)	Avoid
Ibuprofen	(OK)	(OK)	Avoid
Naproxen a	(OK)	(OK)	Avoid

(OK) Data suggest unlikely to cause harm;OK No evidences of harm.

Table II: Migraine Medications and FDA Pregnancy Risk Category

B	C	D	X
Acetaminophen	Aspirin (D in 3rd trimester) Butalbital Amitriptyline Botulinum toxin type A Codeine, Dexamethasone Gabapentin , Keterolac Metoprolol , Naratriptan Nortriptyline , Paroxetine Prochlorpromazine Promethazine, Propranolol Rizatriptan, Sertraline Sumatriptan	Atenolol	Ergots
Doxepin		Divalproex sodium	Methysergide
Fluoxetine		Topiramate	
Caffeine			
Meperidine			
Metoclopramide			
NSAIDs (D in 3rd trimester)			

Federal Drug Administration (FDA) Category B, no evidence of risk in humans; FDA Category C, risk cannot be ruled out; FDA Category D, positive evidence of risk; FDA Category X, contraindicated in pregnancy

Prophylaxis - Women with frequent migraine headaches may require preventative therapy. This may include daily use of beta-blockers and calcium channel blockers in the lowest effective dose, and cognitive and behavioral therapy. If the patient has a coexistent medical condition that requires treatment, a single drug that treats both disorders is ideal.

Beta-blockers such as atenolol, metoprolol, and propranolol are not teratogens, but fetal/neonatal effects from beta-blockade are possible and include: fetal growth restriction and neonatal transient bradycardia, respiratory depression, hyperbilirubinemia, and hypoglycemia. Growth restriction may be more of an issue with atenolol than other beta-blockers.

Short and long acting calcium channel blockers have not been associated with an increased risk of congenital abnormalities, although information is limited.²³ Low dose antidepressants, such as selective serotonin reuptake inhibitors (SSRI) or tricyclic antidepressants (TCA), and antiepileptic medications may also be considered in refractory patients, An older antihistamine agent, cyproheptadine, can be used for acute or prophylactic therapy in pregnant women with migraine.

Tension type Headache - Tension-type headaches feel like pressure or tightness all around the head and have a tendency to wax and wane in intensity. They occur more commonly than migraine headaches, but are less often associated with gastrointestinal upset or heightened sensitivity to light, sound, and smell.³⁵

Tension-type headaches are not likely to improve during pregnancy since they are not hormonally mediated. This theory was supported by a study that noted 48 percent of migraine patients improved during pregnancy compared with only 28 percent of patients with tension-type headaches.¹³

Treatment of tension-type headaches - Acetaminophen is the first line analgesic for treatment of tension-type headaches during pregnancy. NSAIDs are a second line medical therapy. In early pregnancy, an association with miscarriage and some birth defects (cardiac, gastroschisis) has been suggested, but available evidence is limited and weak.³⁶ Combination drugs containing acetaminophen, caffeine, and butalbital with or without codeine, can be administered for short courses; prolonged use should be avoided due to the potential for drug dependency and medication overuse

headaches. Biobehavioral techniques (eg, psychotherapy, relaxation therapy, and biofeedback) are useful in managing chronic tension-type headaches.

Preeclampsia/Eclampsia - Preeclampsia must be considered in every pregnant woman over 20 weeks of gestation with headache. History of Migraine associate with approximately 2X increased risk of pre-clampsia. The risk is approximately 12X in overweight women with migraine.³⁷⁻⁴⁰ Headache is considered a manifestation of severe preeclampsia and a precursor of eclampsia.⁴¹ The exact cause of headache in this disorder is not known, but may be related to increased cerebral perfusion pressure (eg, hypertensive encephalopathy),^{42,43} cerebral ischemia from vasoconstriction,⁴² posterior leukoencephalopathy,⁴⁴ cerebral edema, or microhemorrhages.⁴⁵

Cerebral vascular hemorrhage from malignant hypertension or cerebral venous thrombosis must be considered in women with severe preeclampsia who complain of unremitting headaches. Thrombosis related to an inherited thrombophilia is another possibility.

Neuroimaging studies are indicated in women with a severe headache:

A history of an acute cerebral vascular hemorrhage that occurred during pregnancy, Malignant hypertension, Severe preeclampsia in the setting of preexisting cerebral aneurysm or cerebrovascular arteriovenous malformation, A subacute headache in women with cerebral venous thrombosis.

Postdural Puncture Headache (PDPH)- PDPH occurs when a slow leak of cerebrospinal fluid (CSF) from dural puncture during spinal, epidural, or combined spinal epidural anesthesia leads to contraction of the subarachnoid space and compensatory expansion of the pain-sensitive durally based veins. The pain typically develops within 48 hours of the procedure and is worse on standing or raising the head from the bed and characteristically improves with rest in a supine position; The risk of PDPH is related to the needle diameter, orientation of the needle bevel, and design of the needle tip.⁴⁶ Prophylactic epidural blood patching or saline infusion after dural puncture can decrease the incidence of PDPH,

Posterior Reversible Encephalopathy Syndrome (PRES) - PRES, also known as reversible posterior leukoencephalopathy, is now being recognized as a specific clinical syndrome that can be related to the severe headache associated with preeclampsia. It was first described in 1996 in patients with eclampsia and renal disease, and in patients taking cytotoxic or immunosuppressive drugs.⁴⁴ It is characterized by a headache of acute onset, possibly with seizures, altered mental status (confusion), restlessness, and a spectrum of cortical visual disturbances. PRES is

considered a variant of hypertensive encephalopathy, although an elevation of blood pressure is not required for the diagnosis. The "classic" neuroradiographic findings on magnetic resonance imaging (MRI) of the brain are bilateral, symmetric, T2-hyperintense signal changes in the cortical and subcortical regions, predominantly in the parietal and occipital lobes; CT of the brain may also show similar white matter abnormalities.⁴⁷ PRES is usually reversible with prompt diagnosis and treatment before the development of permanent neurological sequelae or maternal death. The focus of management is aggressive blood pressure control and standard treatment of preeclampsia/eclampsia.⁴⁸

Postpartum Headache -The postpartum period is characterized by sleep deprivation, hormonal changes, irregular food intake, psychological stress, and fatigue. One group retrospectively reported their experience with 95 women with postpartum headache, defined as the onset of severe unremitting headache greater than 24 hours and less than 42 days from the time of delivery.⁴⁹ In this population, the types and frequencies of headache were tension (39 percent), preeclampsia/eclampsia (24 percent), postdural puncture (16 percent), migraine (11 percent), pituitary hemorrhage/mass (3 percent), cerebral venous sinus thrombosis (3 percent), and other (4 percent).

They suggested the following basic guidelines and evaluation:

Preeclampsia/eclampsia should be the initial consideration in women with hypertension and proteinuria. If the woman is normotensive and had regional anesthesia for labor/delivery, an anesthesiologist or neurologist should be consulted for evaluation and treatment of postdural puncture headache. Other types and causes of headache that should be considered include: thunderclap headache, embolic stroke, carotid or vertebral artery dissection, subarachnoid or parenchymal hemorrhage, meningitis, encephalitis, postpartum angiopathy (a reversible vasoconstriction syndrome), primary central nervous system vasculitis, and brain tumor.⁵⁰

Treatment - Acetaminophen, ibuprofen, opioids, caffeine, beta-blockers, calcium channel blockers, prednisone, and most triptans are generally compatible with breastfeeding.⁵¹ Mothers who have ultrarapid CYP2D6 metabolism may have large amounts of opioid in their milk after codeine use; infants of women using opioids should be monitored for sedation. Butalbital, ergotamine, and metoclopramide should probably be avoided because of insufficient information about safety. Aspirin should be avoided because of the theoretical risk of Reye syndrome in the infant.

Evaluation of New Onset Headaches in Pregnancy-Headaches of new onset during pregnancy are uncommon.¹⁷

The possibility of preeclampsia/eclampsia always needs to be excluded. New headaches may be migraine or tension-type headaches, but many other conditions can present with headache at this time. Complaints of chronic headaches may also represent somatization of psychiatric depression that is often under-diagnosed, but commonly found in women.⁵² The differential diagnoses for women with severe headaches (table III) and headaches accompanied by fever (table IV) are different and help guide the work-up. The hypercoagulable state of pregnancy predisposes women with genetic thrombophilias to cerebral venous thrombosis;^{53,54} however, most cerebral venous thromboses occur in women without underlying genetic thrombophilias.

Table III: Characteristic of serious headaches with differential Diagnosis

Characteristics of headache with serious underlying pathology	Differential diagnosis of sudden onset severe headache
History Explosive onset and severe at onset No similar headaches in the past Concomitant infection Altered mental status Headache with exertion Age over 50, Immunosuppression Physical Examination Neurologic abnormalities Decreased level of consciousness Meningismus, Toxic appearance, Papilledema	Subarachnoid hemorrhage Expansion or thrombosis of unruptured intracranial aneurysm, Acute stroke, Subdural and epidural hematomas, Internal carotid and vertebral artery dissection, Cerebral venous thrombosis, Pituitary apoplexy Colloid cyst of the third ventricle Acute expansion of mass lesion in the posterior fossa Hypertensive encephalopathy Spontaneous intracranial hypotension Coital headache, Acute narrow angle glaucoma Exertional headache, Acute sinusitis (with barotrauma), Benign thunderclap headaches

Table IV: Differential diagnosis of headache with fever.

Intracranial infection	Systemic infection	Other causes
Meningitis Encephalitis Brain abscess Subdural empyema	Bacterial infection Viral infection HIV/AIDS Other systemic infection	Familial hemiplegic migraine Pituitary apoplexy Rhinosinusitis Subarachnoid hemorrhage Malignancy of central nervous system

Work-up - Pregnant woman presenting with headache complaints should be evaluated initially with a detailed history and physical examination.⁵⁵ Migraine, tension-type, and cluster headaches are primary headache disorders diagnosed by specific clinical criteria. A woman with a prior history of headaches may continue to suffer from them during pregnancy; pursuing a complicated duplication of diagnostic testing is not necessary if her characteristic symptoms have not changed.

However, a pregnant woman complaining of a headache of sudden onset and intense severity ("worst headache of my life"), especially if not typical of her usual headaches, should be evaluated immediately for preeclampsia or an acute neurovascular event. The presence of new focal neurological signs is also an indication for an in depth evaluation, which may include neuroimaging.⁵⁶

Head computed tomography (CT), if indicated, can be performed during pregnancy without harmful radiation exposure to the fetus. A standard head or cervical spine CT scan exposes the uterus to less than 1 mrad of radiation. An intracranial angiogram also exposes the fetus to less than 1 mrad of ionizing radiation. Magnetic resonance (MR) imaging of the head does not expose the fetus to any radiation and is preferable to CT for assessing nontraumatic or nonhemorrhagic craniospinal pathology, such as edema, vascular disease, mass lesions, or local infection. Suspected arterial vascular lesions can be detected by MR angiography with or without gadolinium contrast. Gadolinium crosses the placental barrier and is excreted by the fetal kidneys without any untoward effects reported to date. However, given the limited experience of its use in pregnancy, gadolinium should be avoided in the pregnant patient unless the potential benefit justifies a theoretical risk to the fetus. MR venogram is the standard for detecting venous thrombosis.

Electroencephalography (EEG) is not routinely obtained for evaluation of headache, but can be used safely in pregnancy in the following settings associated with headache: Suspected clinical or subclinical seizures, alteration or loss of consciousness and suspected encephalopathy.

Summary and Recommendations:

Preeclampsia must be ruled in or out in every pregnant woman over 20 weeks of gestation with headache. Most women with migraine headaches report improvement during pregnancy. For women who request drug therapy, we suggest acetaminophen as first-line acute (abortive) therapy, given its safety profile (Grade B). Women who do not respond to acetaminophen alone may obtain relief with combination therapy such as acetaminophen & metoclopramide); acetaminophen-codeine; or acetaminophen, and butalbital.

Tension-type headaches are not likely to improve during pregnancy since they are not hormonally mediated. We suggest acetaminophen as first-line drug therapy, given its safety profile (Grade B). Non-pharmacologic/behavioral interventions are also useful.

The postpartum period is characterized by sleep deprivation, hormonal changes, irregular food intake, psychological stress, and fatigue, all of which are risk factors for development of headache. Differential diagnosis includes preeclampsia/eclampsia, postdural puncture headache, and tension-type or migraine headache. The presence of focal neurologic signs usually requires neurologic imaging and consultation with a neurologist to rule out a pituitary mass or cerebral venous sinus thrombosis.

Headaches of new onset during pregnancy may be migraine or tension-type headaches, but many other conditions can present with headache at this time pregnant woman complaining of a headache of sudden onset and intense severity ("worst headache of my life"), especially if not typical of her usual headaches, should be evaluated immediately for preeclampsia or an acute neurovascular event. The presence of new focal neurological signs is also an indication for an in depth evaluation.

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