**DRUG SAFETY CONCEPTS**

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# Migraine in Pregnancy
## What are the Safest Treatment Options?

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## Abstract

The occurrence of migraine in women is influenced by hormonal changes throughout the lifecycle. A beneficial effect of pregnancy on migraine, mainly during the last 2 trimesters, has been observed in 55 to 90% of women who are pregnant, irrespective of the type of migraine. A higher percentage of women with menstrual migraine find that their condition improves when they are pregnant. However, in rare cases migraine may appear for the first time during pregnancy.

The positive effects of pregnancy on migraine and the possible worsening *post partum* are probably related to the uniformly high and stable estrogen levels during pregnancy and the rapid fall-off thereafter.

Nondrug therapies (relaxation, sleep, massage, ice packs, biofeedback) should be tried first to treat migraine in women who are pregnant.

For treatment of acute migraine attacks 1000mg of paracetamol (acetaminophen) preferably as a suppository is considered the first choice drug treatment. The risks associated with use of aspirin (acetylsalicylic acid) and ibuprofen are considered to be small when the agents are taken episodically and if they are avoided during the last trimester of pregnancy.

The 'triptans' (sumatriptan, zolmitriptan, naratriptan), dihydroergotamine and ergotamine tartrate are contraindicated in women who are pregnant. Prochlorperazine for treatment of nausea is unlikely to be harmful during pregnancy. Metoclopramide is probably acceptable to use during the second and third trimester.

Prophylactic treatment is rarely indicated and the only agents that can be given during pregnancy are the β-blockers metoprolol and propranolol.

The relationship between migraine and female sex hormones is illustrated by the fact that migraine occurs with a ratio of 2.5 to 1 in women compared with men,[1,2] it is influenced by oral contraceptives[3-5] and it is associated with menstruation in about 7% of women with migraine.[6] Migraine has an overwhelmingly positive course during pregnancy.[7-13]

## 1. Epidemiology

A large percentage of women with migraine[14-16] should be free of migraine symptoms during the second and third trimesters of pregnancy. This is particularly true for women with a previous history of menstrual migraine or with a first manifestation of migraine at menarche.[10,14,15] However, a worsening of migraine is described, usually during the first trimester.[7,9,16] The first appearance of migraine during pregnancy will usually occur in this period and predominantly manifests as migraine with aura.[17] It is controversial whether migraine with aura, in particular, is characterised by an unchanged or even increased frequency of attacks during pregnancy.[14] All in all, an improvement or complete remission is seen in 55 to 90% of women with migraine who become pregnant;[9,14,18,19] however; approximately 25% show no change in the frequency of attacks.[17]

In a retrospective study by Maggioni et al.,[20] 430 women *post partum* were asked about their headache, using the criteria of the International Headache Society (IHS).[21] Of those women, 3% had a headache syndrome which did not fulfil all IHS criteria and 2.3% experienced a secondary headache caused by, for example, hypertension, trauma or toxaemia of pregnancy. Primary headache was experienced by 29.3% of women in the study. Of those, 10% had migraine with aura, 64% migraine without aura and 21% both types of migraine; 26% experienced tension-type headache.

In all 3 groups with primary headache, 80% had either a complete remission or experienced a reduction in the frequency of attacks by over 50% during pregnancy. In all these patients the positive changes started at the end of the first trimester. In only 1 case did the first manifestation of migraine (without aura) occur after the woman became pregnant. In women who were multiparus, 50% showed a similarly good course, but the other half showed an increase in headache frequency with subsequent pregnancies.

Primary headache by itself presents no risk to the fetus, delivery, or to the newborn.[20,22] In the first weeks *post partum* approximately 35 to 40% of women experience headaches,[14,23,24] particularly those women with a previous history of migraine.

## 2. Pathophysiology

The improvement of migraine during pregnancy and the possible worsening *post partum* is probably related to the occurrence of uniformly high and stable estrogen levels during pregnancy and the rapid fall-off thereafter. A similar mechanism probably forms the basis of menstrual migraine,[6,25-27] or the increased incidence of migraine associated with oral contraceptives and with estrogen replacement therapy during the menopause.[15] Another hypothesis concerns the changes in serotonin (5-hydroxytryptamine; 5-HT) metabolism or the raised endorphin levels in the last 2 trimesters.[28,29] The influence of prolactin as a trigger for migraine attacks *post partum* is controversial.[14,30]

Why a migraine is first seen or is worsened during pregnancy cannot be explained on the basis of these pathophysiological hypotheses. In these cases a secondary cause of headache (e.g. subarachnoid haemorrhage, cerebral sinus venous thrombosis, benign intracranial hypertension) must be carefully excluded as differential diagnoses.[15]

## 3. Treatment of Acute or Severe Migraine Attacks

Migraine represents no threat to pregnancy, the fetus or delivery.[16] Usually medical counselling together with nonpharmacological measures (sleep, massage, biofeedback, ice pack) are sufficiently effective in treating migraine attacks during pregnancy.[16] Pharmacological therapy other than simple analgesics should be limited to women in the

second and third trimesters who have frequent and severe attacks accompanied by vomiting and dehydration[14,16] and only then if the benefits clearly outweigh the possible risks to the fetus.

There is little data available with respect to the use of migraine prophylactics and treatment of acute migraine attacks during pregnancy, delivery and lactation.[14] This is because of the obvious ethical limitations on undertaking clinical trials in such a group of patients. Pharmaceutical manufacturers therefore do not generally recommend the use of any drug in pregnancy because of insufficient data. Isolated reports of childhood malformations after taking medication must be considered within the order of the total risks for spontaneous malformations which lies between 2 and 3%.[14,16]

The choice of which drugs to use should take into account the following factors:[16] embryotoxicity, teratogenicity, fetal growth abnormalities and perinatal effects. A summary of drug treatment for migraine during pregnancy is given in table I.[31]

### 3.1 Paracetamol (Acetaminophen)

Paracetamol (acetaminophen) is considered the first choice drug for migraine in pregnancy; 1000mg can be given, preferably as a suppository. There is no evidence of any teratogenic effect. Unlike aspirin (acetylsalicylic acid), paracetamol has only transient adverse effects on the uterus or on platelet function when it is used perinatally.[16]

### 3.2 Aspirin (Acetylsalicylic Acid) and Other Nonsteroidal Anti-Inflammatory Drugs

Worldwide, aspirin, at a dosage of 500 to 1000mg, is the drug most frequently used to treat migraine and other headaches. Aspirin has no teratogenic effects[16,32,33] but in analgesic doses can inhibit uterine contraction and result in increased maternal and newborn bleeding and a narrowing of the ductus arteriosus. Aspirin users generally have a longer duration of gestation and labour than control individuals.[16,34] Because of its effect on the haemostasis of the newborn it should not be used in late pregnancy. However, occasional use by the mother is unlikely to cause adverse effects.

Despite insufficient data, other nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (200 to 400mg) and naproxen (500mg) may be considered.[33-35] Animal studies have shown no evidence of teratogenicity.[14] However, frequent intake of NSAIDs during pregnancy is associated with prolongation of pregnancy and labour, pre-eclampsia, haemorrhagic risks for the mother and fetus[14] and persistent pulmonary hypertension in the neonate. The risks are small when these drugs are taken episodically but, as with aspirin, it is better to restrict their use to the second trimester.

### 3.3 Ergotamine Tartrate and Dihydroergotamine

Ergotamine tartrate and dihydroergotamine are classically contraindicated during pregnancy because of their uterotonic effects.[14,16,22] Ergotamine tartrate is embryotoxic in animals, but there is no evidence of a teratogenic action in humans when administered at the normal dose.[14,16] However, its use is associated with increased perinatal mortality and developmental abnormalities including cleft palate and limb defects.

### 3.4 Sumatriptan, Zolmitriptan and Naratriptan

In the past few years the new selective serotonin 5-$HT_{1B}$ and 5-$HT_{1D}$ receptor agonists, sumatriptan, zolmitriptan and naratriptan, have been approved for the treatment of the acute migraine attack.[36-38] It is thought that serotonin receptor agonists function in migraine by modulating the trigeminovascular system, thereby inhibiting the transmission of pain impulses into the brainstem from the trigeminal nerve to higher parts of the brain.[37] Selective cranio-vascular actions of the 'triptans' would be expected on the basis of the prominent distribution of serotonin receptors in the cranial vasculature. Accordingly, and as only limited data are available, the triptans should currently not be used during pregnancy. There is no evidence that the triptans are human teratogens, but no suf-

ficiently well-controlled studies have been undertaken with pregnant women. To date, there have been no reported abnormalities in babies born to mothers who took sumatriptan during pregnancy.[36]

### 3.5 Antiemetics

Nausea and vomiting are common symptoms of migraine. During a migraine attack, the absorption of orally administered drugs may be delayed. This is possibly due to gastric stasis and may contribute to the failure of some patients' migraine to respond to treatment.[39-41] These pharmacokinetic observations have led to the use of metoclopramide[39,41] and domperidone[40,41] as antiemetic-prokinetic drugs. No teratogenic effects or congenital malformations have been reported with metoclopramide.[16,34,42] Because of the theoretical concerns, it might be wise to avoid its use during the first trimester. Domperidone is a dopaminergic antagonist and there is some experience of this agent from controlled clinical trials in migraine.[41] It crosses the blood-brain barrier poorly and shows variable embryotoxic effects in animal studies.

Several histamine $H_1$ receptor antagonists, e.g. cyclizine and buclizine,[41] are effective in the treatment of nausea/vomiting due to motion sickness. There are no controlled studies substantiating their usefulness in migraine. Their use in pregnancy cannot be recommended.

The antipsychotic prochlorperazine appears not to be associated with detrimental effects in mother and fetus if it used occasionally and in low doses (table I).[16,34,42]

## 4. Migraine Prophylaxis

Prophylactic treatment of migraine is rarely indicated during pregnancy and should be reserved for women with migraine who have long-lasting and frequent attacks where analgesics or other drugs specifically indicated to treat acute attacks have not been sufficiently effective. Possible drugs include β-blockers (propranolol, metoprolol),[43] cyclandelate, flunarizine,[44] valproic acid (sodium valproate),[45] amitriptyline,[46,47] pizotifen[16] and magnesium (table II).[48-50]

Two studies of magnesium in migraine revealed contradictory results.[49,50] Pizotifen, with its diversity of pharmacological properties, precludes a substantial hypothesis concerning its efficacy in migraine prophylaxis.

The data on adverse effects during migraine in pregnancy are limited with respect to amitriptyline.[34,46,47] Limb reduction anomalies have been

**Table I.** Drug treatment for migraine during pregnancy (after MacGregor,[31] with permission)

| Drug | Route/dose | First trimester | Second trimester | Third trimester |
|---|---|---|---|---|
| **Antiemetics** | | | | |
| Domperidone | 10-20mg PO; 30-60 PR | Avoid | Avoid | Avoid |
| Metoclopramide | 10-20mg PO; 20mg PR | Avoid | Possible risk | Possible risk |
| Prochlorperazine | 5-10mg PO; 25mg PR | Possible risk | Possible risk | Possible risk |
| **Analgesics** | | | | |
| Aspirin (acetylsalicylic acid) | 500-1000mg[a] PO EV | Possible risk | Possible risk | Avoid |
| Ibuprofen | 400mg[b] PO | Insufficient data | Insufficient data | Insufficient data |
| Paracetamol (acetaminophen) | 1g[a] PR | No evidence of risk | No evidence of risk | No evidence of risk |
| **Vasoconstrictors** | | | | |
| Ergotamine tartrate | | Contraindicated | Contraindicated | Contraindicated |
| Dihydroergotamine | | Insufficient data | Insufficient data | Insufficient data |
| Sumatriptan, naratriptan, zolmitriptan | | Insufficient data | Insufficient data | Insufficient data |

a Maximum daily dose 2g.

b Maximum daily dose 1.2g.

**EV** = effervescent; **PO** = oral; **PR** = rectal.

**Table II.** Migraine prophylaxis during pregnancy (after MacGregor,[52] with permission)

| Drug | Dosage | First trimester | Second trimester | Third trimester |
|---|---|---|---|---|
| Metoprolol | 100-200mg[a] | Possible risk | Possible risk | Possible risk |
| Propranolol | 10mg tid[b] | Possible risk | Possible risk | Possible risk |
| Flunarizine | 5-10mg[c] | Insufficient data | Insufficient data | Insufficient data |
| Amitriptyline | 10-75mg[c] | Avoid | Possible risk | Avoid |
| Pizotifen | 1-5mg[c] | Possible risk | Possible risk | Possible risk |

a In divided doses or long-acting once daily.

b Up to 160mg in divided doses or long-acting once daily.

c At night.

**tid** = 3 times daily.

reported but not confirmed. It is not recommended during the first and third trimester.

Valproic acid (sodium valproate)[45] is a human teratogen associated with a risk of producing neural tube defects. Animal studies of calcium antagonists suggest that these agents have no teratogenic effects. There is no data available on flunarizine and pregnancy and its adverse effects (depression, bodyweight gain, drowsiness) would limit its potential use during pregnancy.

Propranolol has widely been taken for the treatment of hypertension or eclampsia during pregnancy without evidence of teratogenicity. It is debatable whether the fetal and neonatal adverse effects that have been reported in the offspring of women taking propranolol during pregnancy[51,52] are due to propranolol, disease in the mother, or to other drugs. Most case reports show associations with growth retardation, hypoglycaemia, hypocalcaemia, bradycardia and respiratory depression. No fetal malformations have been reported with metoprolol to date.

## 5. Conclusion

Ideally, drugs should be avoided during pregnancy and migraine attacks should be prevented and treated by nondrug methods. For treatment of acute migraine, paracetamol is the only drug that can, at present, be recommended for use throughout pregnancy and breastfeeding. For nausea, prochlorperazine and metoclopramide are probably acceptable for use during the second and third trimesters. The use of prophylactics should be restricted, but, if necessary, metoprolol and propranolol have the greatest weight of data assessing their safety during pregnancy.

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