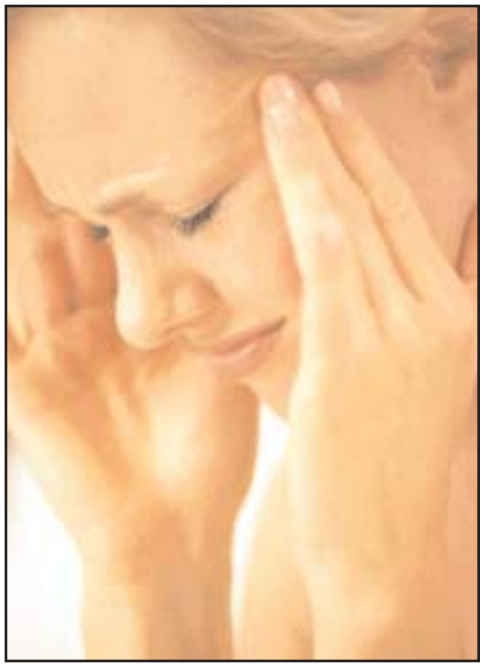

# Mastering Migraine and Women's Related Issues

Migraine in women poses a series of specific and challenging questions, which need to be addressed to optimize the treatment.

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Between 15% and 17% of Canadian women are afflicted with migraine at some point in their lives.[1] Several internal and external factors can modulate the frequency and severity of the condition. In women, variations in the hormonal milieu—from puberty to menopause—have a definite influence in the clinical expression of migraine.

Migraine is more likely to be active at the time of menses, and for most women with migraine, pregnancy is associated with a reduced number of attacks. There are several ways to attenuate the potential effects on the infant that medications taken during breastfeeding for the treatment of migraine may have. Menopause can become a critical period, with an increase in the frequency of attacks in the perimenopausal period, and, in some cases, perpetuation of the problem after menopause with hormonal replacement therapy.

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## Migraine and Oral Contraception

Oral contraceptives (OCs) may be associated with the development of primary headache disorders. One uncontrolled study has shown that as many as 10% of women taking an estrogen preparation containing more than 50 mcg of ethinylestradiol (EED) had developed *de novo* headaches.[2] This study was carried out before the International Headache Society diagnostic criteria for headache

**Table 1**

**Incidence of Ischemic Stroke in Young Women (less than 45 years)†**

| | Odds Ratio | |
|---|---|---|
| Non-OC + Non-migraine | | 6/100,000 women-years |
| OC + Non-migraine | X 3 | 18/100,000 women-years |
| OC + Migraine without aura | X 9 | 54/100,000 women-years |
| OC + Migraine with aura | X 27 | 162/100,000 women-years |

† = Assuming that independent odds ratio are multiplicative

disorders had become available.[3] It is, therefore, difficult to determine the type of these *de novo* headaches. In more recent studies, it appears that the incidence of new onset headache with OCs correlate with the dosage in EED.[4] New onset headaches were reported in less than 2% of women taking an OC with 20 mcg of EED. Newer OCs usually contain 30 mcg of EED and are combined with third-generation progestogens, which seem to have less negative influence on the occurrence of headaches.

*Menstrually associated migraine should be treated in the same way as regular migraine; that is, by using a strategy of staged care or stratified care.*

The influence of OCs in already diagnosed migraineurs is quite variable.[5] Thirty-nine per cent to 65% of women will experience no change; a small number (3% to 35%) will show improvement; and between 18% and 50% will develop worse migraine headaches, particularly in the drug-free interval. A worsening migraine condition with OC use is usually observed in the first cycles; more often in women with a family history of migraine. The effect of discontinuing the OC on resuming a previously lower frequency of migraine headaches remains totally unpredictable.

OCs have been associated with an increased risk of ischemic stroke. Odds ratios for ischemic stroke range from 1.5 to 3.2 with pills containing 50 mcg of EED, and increases with higher concentrations in EED.[6] Migraine and predominantly migraine with aura also have been associated with an increased risk of ischemic stroke. The odds ratio could range from a maximum of three in migraine without aura to 6.2 in migraine with aura.[7] The risks of ischemic strokes in migraineurs increase further with heavy smoking (20 cigarettes/day), age and OC use. As a useful clinical approximation, one can say that OCs do increase the incidence of ischemic strokes in young women by a factor of three, and that migraine in itself is an independent risk factor.

The odds ratio for independent risk factors may be multiplicative. As an example, the odds

ratio for ischemic stroke in a young woman with migraine with aura taking low-dose estrogen OC could be: 3 x 6 = 18 (Table 1). The absolute risk of ischemic stroke in young women remains low: 6/100,000 women-years in non-migrainous women and 19/100,000 women-years in migrainous women. Consequently, there is no absolute contraindication to the use of OCs in women with migraine without aura and without risk factors.[8] Caution should be exercised in prescribing OCs to women with migraine with aura, and OCs should be discontinued in women with migraine without aura, who develop simple or complex auras, as well as in women with migraine with simple aura, who develop complex or prolonged aura.

Progestogen-only hormonal contraceptive use has not been associated with an increased risk of ischemic stroke. Progestogen-only hormonal contraception should be considered as an alternative in high-risk situations.

## Migraine and the Menstrual Cycle

Menstrual migraine is not defined as such by the International Headache Society. Menstrual migraine is usually defined as a migraine attack starting from two days before menses to the last day of menstruation. Only about 9% of women with migraine will get their attacks exclusively with menses. Most of the women with migraine (60%) will get menstrually associated migraine and intermenstrual migraine. Several women with menstrual migraine will tend to be symptomatic at the time of ovulation. The susceptibility to migraine throughout the menstrual cycle seems to

**Table 2**

**Perimenstrual Migraine Treatment Protocols (7-10 days/month)**

- Naproxen 500 mg bid
- Mefenamic acid 250 mg tid
- Ergotamine 1 mg bid
- Naratriptan 1 mg bid
- Hormonal therapy:
  - Estradiol gel 1.5 mg qd
  - Estradiol patch 100 mcg q 3-4 days

Table 3

**Pharmacologic Treatment of Migraine in Pregnancy**

| Symptomatic Treatment | | Prophylactic treatment |
|---|---|---|
| First Choice: | Acetaminophen<br>Codeine | Propranolol |
| †Second Choice: | Acetylsalicylic acid<br>NSAIDs (naproxen, ibuprofen) | Amitryptiline |
| Severe Attacks: | Chlorpromazine<br>Dimenhydrinate<br>Meperidine<br>Morphine<br>Prednisone<br>Dexamethasone | |

†Should not be used in the third trimester

be closely linked to falling levels of circulating estrogens. Estrogen withdrawal and release of prostaglandins at the time of menstruation, through several mechanisms, tend to alter pain perception.[9]

Menstrually associated migraine often has been considered as more severe and more difficult to treat than the intermenstrual migraine. This notion arises from the fact that menstrually associated migraine tends to be more prolonged, with more recurrence after symptomatic treatment. These observations, however, have not been validated by specific clinical studies.

Menstrually associated migraine should be treated in the same way as regular migraine; that is, by using a strategy of staged care (prospective treatment according to the severity of the attack) or stratified care (treatment according to the usual disability from attacks).

Several perimenstrual prophylactic treatment protocols have been proposed (Table 2). The treatment is usually given for a period of seven to 10 days, starting two to three days before the time of menstruation. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen (500 mg bid) or mefenamic acid (250 mg tid), ergotamine tartrate 1 mg bid, and naratriptan 1 mg bid, have been used as perimenstrual prophylactics. The best results, however, seem to have been obtained with the percutaneous use of estradiol gel 1.5 mg daily or estradiol patches 100 µg every three to four days.

## Migraine and Pregnancy

Migraine is not a risk factor for the pregnancy or the fetus.[10] Despite the fact that up to 50% of the pregnancies are unplanned, and that many migraineurs may continue to treat their headaches with their usual medications in the early phase of their pregnancy, no increased incidences of toxemia, abnormal labor, stillbirths or congenital malformation have been reported in pregnant women with migraine.

Migraine, however, remains a risk factor for

**Table 4**

**Pharmacologic Treatment of Migraine During Breastfeeding**

| Symptomatic treatment | | Prophylactic treatment | |
|---|---|---|---|
| *Use* | *Avoid* | *Use* | *Avoid* |
| Acetaminophen | Meperidine | Tricyclics | Atenolol |
| Ibuprofen | Oxycodone | Propranolol | Nadolol |
| Flurbiprophen | High doses ASA | | Sotalol |
| Ketorolac | Ergotamine | | |
| Mefenamic acid | | | |
| Sumatriptan | | | |
| Morphine | | | |
| Prednisone | | | |

migraine in the offspring. Although the genetics of migraine have not been sorted out, several longitudinal studies have shown a definite inheritance of migraine, with the condition being transmitted more readily from the mother than from the father.

During pregnancy, migraine generally tends to improve in 60% to 70% of the cases and mostly in the second and third trimester. Improvement is observed predominantly in women with a history of perimenstrual migraine or migraine onset at menarche. Migraine can, at times, worsen during pregnancy (4% to 8%), particularly in women with migraine with aura. In 10% of cases, migraine may start with pregnancy, and the new-onset migraine type often is migraine with aura. Most women who experience improvement in their migraine condition during pregnancy will soon resume their pre-pregnancy pattern in the immediate post-partum.

The management of migraine during pregnancy should primarily be non-pharmacologic. Should a pharmacologic approach become necessary, several medications are considered safe for use (Table 3).

For attacks of moderate-to-severe intensity, acetaminophen and codeine are the drugs of choice. Acetylsalicylic acid (ASA) and NSAIDs (ibuprofen and naproxen) also can be used, except in the third trimester, where they have been associated with pre-eclampsia, prolonged labor, pulmonary hypertension and increased hemorrhagic risk for both the mother and the fetus. For attacks of severe or ultrasevere intensity, in addition to general measures, such as rest and hydration, chlorpromazine and dimenhydrinate can be used; for pain control, meperidine, morphine, prednisone and dexamethasone can be considered.

*If an increased frequency of attacks becomes an issue, prophylactics, such as propranolol or amitryptiline, are safe. They should be discontinued, however, two weeks before the end of pregnancy.*

If an increased frequency of attacks becomes an

Table 5

**Optimal Use of Hormone Replacement Therapy in Migraine**

| Estrogens | Progestins |
|---|---|
| Reduce estrogen dose | Switch from cyclic to continuous lower dose |
| Switch from qd to bid dosage | Change progestin type |
| Convert from interrupted to continuous dosing monitoring) | Discontinue progestin (requires endometrial |
| Change conjugated estrogen to pure estradiol, synthetic estrogen or pure estrone | Change delivery system (orally to vaginal) |
| Convert from oral to parenteral dosing | |
| Add androgens | |
| Switch to selective estrogen receptor modulators | |

issue, prophylactics, such as propranolol or amitryptiline, are safe. They should be discontinued, however, two weeks before the end of pregnancy.

## Migraine and Breastfeeding

Treatment of migraine in a breastfeeding woman raises several questions. How much of a given drug will be secreted in milk? What are the potential side effects for the infant? For any drug, the infant dose can be calculated according to a formula that takes into account maternal absorption, the concentration ratio of milk to maternal plasma, and the infant clearance of the drug. A drug taken by the mother is considered to give the infant a non-clinically significant level of exposure if the blood levels of the given drug are less than 10% of the weight-adjusted therapeutic dose for the infant.[11] Most drugs would give an exposure of much less than 10%. The effect on the infant can be minimized by asking the mother to take her medication after breastfeeding.

For the symptomatic treatment of migraine during breastfeeding, several medications can be used (Table 4). Some medications, however, should be avoided: meperidine may induce transient behavioral changes; oxycodone gives an exposure that approaches 10%; ergotamine reduces prolactin secretion; and high doses of ASA may produce transient metabolic acidosis in the infant. The tricyclic antidepressants and propranolol can be used safely, but atenolol, nadolol and sotalol should be avoided, as they may give a level of exposure close to 10%.

## Migraine and Menopause

Classically, menopause is considered a critical period in the life of a migraineur. Before showing a tendency to abate after menopause, migraine may show an acceleration in frequency and severity during the early phase of menopause. That seems to be true predominantly in women with a previous history of menstrual migraine. There are, however, few studies that have addressed this problem in detail. In contrast, migraine may be worsened after surgical menopause.[12]

The symptoms of migraine may be relieved with hormone replacement therapy (HRT) in the perimenopause, where frequent and unpredictable

fluctuations in the estrogens are seen. During the early phase of menopause, HRT may tend to normalize the circulating levels of estrogens. In contrast, HRT may aggravate migraine in the postmenopause.

There are, however, several ways whereby such a tendency could be attenuated.[13] Conjugated estrogens are known to produce more negative effects than the synthetic ones or pure estradiol. The dosage of estrogens may need to be reduced, switched from a daily to a twice daily schedule, or converted from an interrupted to a continuous dosing. A parenteral dosing often produces less negative effects than an oral one. Adding androgens to estrogens or switching to selective estrogen receptor modulators may be appropriate in some patients. Similarly, modifications in progestin dosing may be considered (Table 5).



Although, in some patients, HRT may have a negative effect on their migraine condition, there is no evidence that it increases the risk of ischemic stroke. Moreover, in contrast with the observations in women younger than 45 years, there is no evidence that migraine is a risk factor for ischemic stroke in women over age 45.[6,8]

## Conclusion

Migraine in women poses a series of specific and challenging questions, which need to be addressed to optimize treatment. One can no longer consider OCs as absolutely contraindicated in patients with migraine. Ways to treat disabling menstrual migraines are available and should be used. Migraine also can be safely managed both during pregnancy and breastfeeding. Finally, menopause may not represent a pause for migraine in many women, and many different treatment protocols render HRT possible, when indicated. CME

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