Migraine in pregnancy and lactation: a clinical review

E Anne MacGregor

Overview
Migraine affects mostly women during their reproductive years and is far more prevalent than many people realise. Within 1 year, over 15% of women and 6% of men have attacks of migraine with or without aura. Although migraine without aura accounts for the majority of migraines in women, the overall 1-year prevalence of migraine with aura is around 5% for women and 2% for men. Migraine prevalence varies with age, rising through early adult life, peaking at age 30–40 years and then declining in the late 40s and after 50 years in both males and females. Drug treatment is usually necessary for effective control of migraine hence many women who are pregnant or planning a pregnancy will want to know what effects pregnancy will have on migraine and vice versa, and what treatments they can take safely during pregnancy and lactation.

Search strategy
A MEDLINE search using the search terms ‘migraine’ and ‘pregnancy’ identified 389 publications. The Cochrane search strategy for identifying reports of randomised controlled trials was run on this database. The search strategy identified 109 publications, which were scrutinised for relevancy to this review.

In addition, references from the author’s own files, a hand-search of the journals Cephalalgia and Headache, and peer-reviewed presentations at international congresses were also considered.

Planning a pregnancy
Drugs and other teratogens exert their greatest effects on the fetus in the first trimester, often before the woman knows she is pregnant. Drug use during pregnancy is common, each woman taking an average of four to five different medications. Although some of these, such as iron and vitamin supplements, are specifically recommended in pregnancy, analgesics, anti-emetics and antacids are also widely used by women, with or without migraine.

Given that migraine is a condition of the reproductive years, health care professionals are well placed to help women consider management options for planned pregnancies. If women are taking preventative treatments that are not recommended in pregnancy, they should be advised to consider stopping them and/or switching to a safer alternative. For drugs used to treat the symptoms of migraine, the aim should be to try to limit triptans to the first 2 weeks of the menstrual cycle, when the woman is unlikely to be pregnant. To reduce the risk of neural tube defects, all women of childbearing age should ensure a dietary intake of 400 µg folate acid daily, with supplements as required, increasing to 600 µg during pregnancy.

Women with migraine receiving assisted conception would particularly benefit from support and advice on management as treatment with gonadotrophin-releasing hormone analogues is frequently associated with headache.

Headache can be symptomatic of emotional stress. Frequent pre-pregnancy headache is a strong predictor of poor general and emotional health during pregnancy and should alert the health care professional to assess these women for depressive disorders.

Effect of pregnancy on migraine
Retrospective and prospective studies suggest that around 60–70% of migraineurs experience improvement in migraine during pregnancy; in around 20% attacks completely disappear (Table 1 and Figure 1). If migraine has not improved by the end of the first trimester it is likely to continue throughout pregnancy and postpartum.

Migraine without aura
Women with pre-existing migraine without aura generally report improvement or cessation of migraine during pregnancy. Respite is greater for women with a history of menstrual or menstrually related migraine without aura than for women with no evidence of a menstrual association.

Migraine with aura
In contrast to migraine without aura, women who have pre-existing migraine with aura are more likely to continue to have attacks during pregnancy. Women with pre-existing migraine without aura may develop migraine without aura than for women with no evidence of a menstrual association.

Effect of migraine on pregnancy
In general, women can be reassured that migraine, either with or without aura, does not have any adverse effects on the outcome of pregnancy in otherwise healthy women (Table 2). However, studies have been retrospective, with consequent potential error due to confounding and recall bias, and numbers included in the studies have been small with few data from large epidemiological studies. Banhidy et al. examined the risk of congenital abnormalities in infants born to women who had migraines and other headaches during pregnancy. They evaluated 38 151 newborn infants without any abnormalities and 834 controls with Down syndrome. Migraine during pregnancy was not associated with any increased risk of congenital abnormalities. No increased risk was found for first trimester migraines or for migraines in the second or third trimester. 45 The risk of congenital abnormalities in infants born to women who had migraines and other headaches during pregnancy was not increased compared to the control group.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Sample size</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lance and Anthony (1966)</td>
<td>Retrospective</td>
<td>120 women with pre-existing migraine/252 pregnancies</td>
<td>Improvement or complete remission: 58%</td>
<td>Improvement related to past MM: 64% MM vs 48% non-MM Lack of improvement more frequent for non-MM: 36% MM vs 52% non-MM</td>
</tr>
<tr>
<td>Somerville (1972)</td>
<td>Retrospective</td>
<td>38 women with migraine during pregnancy</td>
<td>Improvement or complete remission: 63% (18.5% complete remission)</td>
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</tr>
<tr>
<td>Manzoni et al. (1986)</td>
<td>Retrospective</td>
<td>74 women with migraine who had at least one pregnancy: 36 MO, 38 MA</td>
<td>Improvement related to past MM: 86% MM vs 60% non-MM (p = 0.02) Lack of improvement more frequent for non-MM: 7% MM vs 15% non-MM Lack of improvement more frequent for aura (p = 0.06)</td>
<td></td>
</tr>
<tr>
<td>Ratinahirana et al. (1990)</td>
<td>Retrospective survey 1–3 days postpartum</td>
<td>703 women 116 with migraine: 90 MO, 26 MA</td>
<td>Improvement related to past MM: 86% MM vs 60% non-MM (p = 0.02) Lack of improvement more frequent for non-MM: 7% MM vs 15% non-MM Lack of improvement more frequent for aura (p = 0.06)</td>
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</tr>
<tr>
<td>Rasmussen and Olesen (1992)</td>
<td>Retrospective</td>
<td>1000 people of which those who had been pregnant: 21 MA, number not stated MO</td>
<td>Improvement related to past MM: 86% MM vs 60% non-MM (p = 0.02) Lack of improvement more frequent for non-MM: 7% MM vs 15% non-MM Lack of improvement more frequent for aura (p = 0.06)</td>
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<tr>
<td>Granella et al. (1993)</td>
<td>Retrospective</td>
<td>1300 women with migraine: 571 with migraine before first pregnancy</td>
<td>Improvement related to past MM: 86% MM vs 60% non-MM (p = 0.02) Lack of improvement more frequent for non-MM: 7% MM vs 15% non-MM Lack of improvement more frequent for aura (p = 0.06)</td>
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</tr>
<tr>
<td>Chen and Leviton (1994)</td>
<td>Prospective</td>
<td>484 women with migraine at prenatal visit</td>
<td>Improvement related to past MM: 86% MM vs 60% non-MM (p = 0.02) Lack of improvement more frequent for non-MM: 7% MM vs 15% non-MM Lack of improvement more frequent for aura (p = 0.06)</td>
<td></td>
</tr>
<tr>
<td>Cupini et al. (1995)</td>
<td>Comparative</td>
<td>268 women: 180 MO, 88 MA; 116 MO and 35 MA had had pregnancies, 104 MO and 30 MA were already suffering from migraine at first pregnancy</td>
<td>Improvement related to past MM: 86% MM vs 60% non-MM (p = 0.02) Lack of improvement more frequent for non-MM: 7% MM vs 15% non-MM Lack of improvement more frequent for aura (p = 0.06)</td>
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</tbody>
</table>

M, migraine; MA, migraine with aura; MM, menstrual migraine; MO, migraine without aura; NA, not applicable; NR, not reported; NS, not significant; TH, tension headache.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Sample size</th>
<th>Outcome</th>
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<tbody>
<tr>
<td></td>
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<td>Improvement or complete remission</td>
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<tr>
<td>MacGregor et al. (1997)</td>
<td>Retrospective questionnaire</td>
<td>100 women; 30 with migraine before first pregnancy</td>
<td>53%</td>
</tr>
<tr>
<td>Scharff et al. (1997)</td>
<td>Prospective diary</td>
<td>30 women with headaches ≥2 per month</td>
<td>56.7% (NS)</td>
</tr>
<tr>
<td>Maggioni et al. (1997)</td>
<td>Retrospective questionnaire</td>
<td>430 women 3 days postpartum 81 MO, 12 MA, 33 TH</td>
<td>In all three groups: 80% had ≥50% headache reduction</td>
</tr>
<tr>
<td>Marcus et al. (1999)</td>
<td>Longitudinal prospective</td>
<td>49 women: 16 M; 16 TH; 15 M+TH</td>
<td>30% improvement between second and third trimesters (NS)</td>
</tr>
<tr>
<td>Granella et al. (2000)</td>
<td>Retrospective case control</td>
<td>100 MA; 200 MO controls</td>
<td>MO 76.8% MA 43.6% OR 0.2 (95% CI 0.1–0.5)</td>
</tr>
<tr>
<td>Sances et al. (2003)</td>
<td>Prospective diary</td>
<td>49 women with migraine during 3/12 before pregnancy: 47 MO; 2 MA</td>
<td>MO first trimester 46.8% (10.6% complete remission)</td>
</tr>
<tr>
<td>Kelman (2004)</td>
<td>Retrospective questionnaire</td>
<td>504 women with migraine: 61.3% had a pregnancy</td>
<td>38.2% (20.4% complete remission)</td>
</tr>
<tr>
<td>Melhado et al. (2005)</td>
<td>Prospective cohort</td>
<td>993 pregnant women with headaches prior to gestation 332 women reported MM; 516 reported non-MM</td>
<td>Of women with MM, 62% during the first trimester; 74% during the second trimester; 78% during the third trimester</td>
</tr>
<tr>
<td>Erttesvag et al. (2005)</td>
<td>Prospective questionnaire</td>
<td>1631 pregnant women</td>
<td>58%</td>
</tr>
</tbody>
</table>

M, migraine; MA, migraine with aura; MM, menstrual migraine; MO, migraine without aura; NA, not applicable; NR, not reported; NS, not significant; TH, tension headache.
pregnancy affected 565 (2.5%) mothers of the group with congenital abnormalities vs 713 (1.9%) mothers in the normal group. Of all the parameters studied, the only positive finding was that limb deficiencies were associated with a higher rate of maternal malignancies during the first trimester of pregnancy, for both the congenital abnormalities group vs matched normal group (adjusted POR 2.5, 95% CI 1.1–5.8) and the congenital abnormalities group vs Down syndrome controls (adjusted POR 1.7, 95% CI 1.3–3.0). Although this study has the benefit of large numbers, these data are not confirmatory and the effect of other independent variables, drug and non-drug treatments taken, and misdiagnosis of conditions mimicking migraine cannot be ruled out.

In women presenting with aura for the first time during pregnancy, the clinician should consider other disorders such as thrombocytopenia, cerebral venous sinus thrombosis or imminent eclampsia, which may present with symptoms not dissimilar from migraine. Headache with eclampsia can be associated with visual changes, including blurred vision, scotomata or bright flashing lights. To avoid incorrect diagnosis and ensure optimum treatment, a careful history and examination are mandatory.

There is an increasing body of evidence to support an association between migraine, pre-eclampsia and eclampsia. A recent case control study of 244 women with pre-eclampsia and 470 normotensive controls found that a history of migraine was associated with a 1.8-fold increased risk of pre-eclampsia (95% CI 1.1–2.7). Women who were 30 years or over when diagnosed with migraine had the highest risk (OR 2.8, 95% CI 0.8–9.0). Overweight migrainous women, compared with lean non-migrainous women, had a 12-fold increased pre-eclampsia risk (95% CI 5.9–25.7).

Postpartum
Headache is common in the week following delivery, affecting around 30–40% of women. If there is any doubt about the diagnosis, rare causes such as cerebral venous thrombosis should be excluded. Cerebral venous thrombosis is estimated to occur in 1 per 2500 to 10 000 deliveries and is most likely in women with hypercoagulability. It usually presents with neurological deficits, although severe progressive headache is reported in thrombosis of the superior sagittal sinus.

The risk of cerebral infarction, although not increased during pregnancy itself, is increased in the 6 weeks after delivery. Results from a recent study suggest that the risk is greater for women with a history of migraine (OR 16.9, 95% CI 9.7–29.5) as well as women with pre-eclampsia and gestational hypertension (OR 4.4, 95% CI 3.6–5.4). However, evidence is limited and prospective cohort studies are needed to confirm these findings.

Lactation generally leads to an improvement in the clinical course of migraine headache during the postpartum period. A longitudinal prospective study of headache during pregnancy and postpartum found that the headache index during the first three postpartum months was similar for patients who breastfed to that obtained during the second trimester of pregnancy. These data suggest that the improvement of migraine commonly seen during the second trimester of pregnancy continues into the postpartum time period if breastfeeding is maintained. A more recent study reported that migraine recurred within the first postpartum month in 100% of women who bottle-fed and in only 43.2% of those who breastfed (p = 0.0003).

Pathophysiology
Fluctuations in estrogen levels, particularly declining levels after a stable estrogen state, are known to increase migraine in some susceptible women. Hence it might be expected that the high, stable levels of placental estrogen during the second and third trimesters of pregnancy would have a beneficial effect on migraine without aura. Immediately following delivery, estrogen levels rapidly fall, which could account for increased postpartum migraine. The protective effect of breastfeeding probably relates to stable low levels of estrogen since lactation inhibits ovulation. The mean time to ovulation after delivery is 189 days in breastfeeding women and 45 days in non-breastfeeding women. Resumption of ovulation and menstruation is associated with a return to pre-pregnancy patterns of migraine.

However, it is unlikely that the mechanism of migraine without aura relates solely to falling estrogen levels and there are many physical, biochemical and emotional changes in pregnancy that could account for improvement. It has been noted that pregnancy is associated with a state of analgesia, resulting from estrogen and progesterone working in combination to modulate opioid activity. Other relevant effects of the pregnant state include increased muscle relaxant and reduced platelet aggregability. In susceptible women, high plasma concentrations of estrogen are associated with increased risk of migraine with aura. One mechanism that could account for this is the development of platelet hyperaggregation.

Investigations during pregnancy and lactation
Radiological imaging is usually normal in migraine and is rarely helpful other than when indicated to exclude suspected secondary headache resulting from underlying pathology. Should investigations be required in pregnancy, such as for women presenting with atypical features of migraine or prolonged focal symptoms, they are the same as for non-pregnant women. Diagnostic investigations in pregnant patients should be as thorough as in non-pregnant patients and there is no reason to defer radiological testing purely on account of the pregnancy.

Interventions
Identification of non-hormonal triggers
Despite the strong association between hormones and migraine, identification and elimination of non-hormonal trigger factors still plays an important part in management. Assuming the concept of multiple factors acting in combination to trigger migraine, hormonal factors combine with non-hormonal triggers to increase the overall susceptibility to attacks. Therefore, every effort should be made to identify and eliminate non-hormonal triggers. Women should be encouraged to avoid skipping meals, take regular exercise, drink plenty of fluids and try to maintain a regular sleep pattern.

Drugs in pregnancy
To avoid the potential for drug-related effects on pregnancy, it is important to minimise drug exposure in any woman who is planning pregnancy or who is at high risk of unplanned pregnancy. If possible, prophylactic medication should be discontinued and strategies for the management of acute attacks discussed. As few drugs as possible should be...
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Sample size</th>
<th>Outcome</th>
<th>Worsened</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wainscott et al. (1978)15</td>
<td>Case control</td>
<td>777 women with migraine vs 183 controls</td>
<td>Miscarriage, stillbirth, toxaemia of pregnancy, congenital malformations</td>
<td>No difference between migraineurs and controls</td>
<td>Similar outcome to national average Suggests neither migraine nor drugs commonly used for migraine affect outcome</td>
</tr>
<tr>
<td>Moore and Redman (1983)19</td>
<td>Case control</td>
<td>24 women with severe eclampsia &lt;34/40 vs 48 age and parity matched controls</td>
<td>Migraine as a risk factor for early onset pre-eclampsia</td>
<td>Migraine associated with increased risk of pre-eclampsia</td>
<td></td>
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<tr>
<td>Marcoux et al. (1992)20</td>
<td>Case control</td>
<td>426 cases (172 pre-eclampsia; 254 gestational hypertension) vs 505 controls</td>
<td>Likelihood of migraine in the year before pregnancy in cases vs controls</td>
<td>Migraine associated with increased risk of pre-eclampsia: OR 2.44 (95% CI 1.42–4.20) Migraine associated increased risk of gestational hypertension: OR 1.70 (95% CI 1.02–2.85)</td>
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<tr>
<td>Olesen et al. (2000)45</td>
<td>Case control</td>
<td>115 pregnant women with migraine vs healthy pregnant controls</td>
<td>Risk of preterm delivery and low birth weight</td>
<td>Risk of low birth weight was increased: OR 3.0 (95% CI 1.3–7.0) for migraineurs who delivered at term vs controls</td>
<td></td>
</tr>
<tr>
<td>Facchinetti et al. (2005)21</td>
<td>Case control</td>
<td>75 cases with recent pre-eclampsia vs 75 controls with uneventful pregnancy at term</td>
<td>Headache in cases vs controls</td>
<td>Headache in 47/75 with pre-eclampsia vs 19/75 controls OR 4.95 (95% CI 2.47–9.92)</td>
<td></td>
</tr>
<tr>
<td>Adeney et al. (2005)24</td>
<td>Case control</td>
<td>244 cases with pre-eclampsia vs 470 normotensive controls</td>
<td>Risk of pre-eclampsia</td>
<td>Migraine associated with increased risk of pre-eclampsia: OR 1.8 (95% CI 1.1–2.7)</td>
<td></td>
</tr>
<tr>
<td>Banhidy et al. (2006)17,23</td>
<td>Case control</td>
<td>22 843 cases with congenital abnormalities vs 38 151 normal controls and 834 controls with Down syndrome (malformed control)</td>
<td>Prevalence of severe migraine during pregnancy in the mothers</td>
<td>Migraine during pregnancy occurred in 565 (2.5%) mothers of cases vs 713 (1.9%) mothers of normal controls and 24 (2.9%) mothers of malformed controls</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Observational study</td>
<td>2850 pregnancy-related strokes from the Nationwide Inpatient Sample 2000–2001</td>
<td>Incidence and risk factors for stroke in pregnancy and the puerperium</td>
<td>Rate of migraine in mothers of cases with congenital abnormalities vs controls</td>
<td>Severe migraine associated with increased risk of pre-eclampsia and severe nausea/vomiting No difference in proportion of low birth weight and preterm births</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All congenital abnormalities: POR migraine 1.3 (95% CI 1.2–1.5) vs normal controls; POR 0.9 (95% CI 0.6–1.3) cases vs Down syndrome controls Limb deficiencies POR first trimester migraine 2.5 (95% CI 1.1–5.8) vs normal controls; POR 1.7 (95% CI 1.3–3.0) cases vs Down syndrome controls</td>
<td>Data from the large Hungarian Case-Control Surveillance of Congenital Abnormalities Study suggest increased risk of congenital limb deficiencies with severe maternal migraine in first trimester, which may not be identified in small studies. This finding needs to be confirmed in other studies</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio; POR, prevalence odds ratio.
used, which have the least potential to cause damage, in the
lowest effective dose. Although many of the drugs taken by
unsuspecting pregnant women rarely cause harm, there is a
difference between reassuring the pregnant woman that what
she has taken is unlikely to have affected the pregnancy and
advising her what she should take for future attacks. Most
evidence of safety is circumstantial; few drugs have been
tested during pregnancy and lactation because of the obvious
ethical limitations of undertaking clinical trials. This lack of
data means that use of most drugs in pregnancy is unlicensed.
Drugs should only be considered if the potential benefits to the
woman and fetus outweigh the potential risks. The woman
should be given sufficient information about any known
risks, and make her own decision about its use, with
clear documentation of the discussion.

In the UK, further advice is available from local drug
information centres and from the National Teratology
Information Service (see Further Information).

Symptomatic treatment
The treatment of migraine during pregnancy is the same as
for the non-pregnant state, with some exceptions (Table 3).

Analgesics
Acetaminophen/paracetamol: Despite lack of formal
clinical trial evidence, paracetamol has been used for over
40 years and there is substantial information on the safety of
therapeutic doses in pregnancy. It is the analgesic of choice
for the short-term relief of mild to moderate pain and
pyrexia during pregnancy. Aspirin: Clinical and epidemiological data from large
numbers of women who have taken analgesic doses of
aspirin during pregnancy provide evidence of its safety in the
first and second trimesters. It should be used with caution near term as its effect on platelet function increases
the risk of prolonged labour, postpartum haemorrhage and
neonatal bleeding. In common with non-steroidal anti-
inflammatory drugs (NSAIDs), aspirin may be associated
with premature closure of the fetal ductus arteriosus.

Codeine: Codeine is not generally recommended for the
management of migraine in the UK. However, occasional
use in doses found in combined analgesics is unlikely to
cause harm.

NSAIDs
There are insufficient data to support the use of NSAIDs
other than ibuprofen, which can be given in doses not
exceeding 600 mg daily. The available data do not indicate that exposure to ibuprofen before 30 weeks of
pregnancy is associated with an increased risk of
malformations or spontaneous miscarriage. If an NSAID is
required in the first or second trimester, ibuprofen would be
the preferred agent. However, chronic exposure or exposure
to high doses after 30 weeks is associated with an increased
risk of premature closure of the ductus arteriosus and
oligohydramnios. This is related to the inhibitory effect of
ibuprofen on prostaglandin activity. In circumstances where
the clinical condition requires treatment with NSAIDs
during the third trimester, the fetus should be monitored
regularly to detect any potential adverse effects.

Anti-emetics
Buclizine, chlorpromazine, cyclizine, domperidone,
metoclopramide and prochlorperazine have been used
widely in pregnancy without reports of adverse effects.

Ergots
Ergotamine and dihydroergotamine are contraindicated as
uterine hypertonicity and vascular disruption increase the
risk of miscarriage.

Triptans
All seven triptans (almotriptan, eletriptan, frovatriptan,
naratriptan, rizatriptan, sumatriptan and zolmitriptan) are
available on prescription in the UK. Sumatriptan is also
available without prescription from pharmacies.

Safety of triptans during pregnancy has yet to be
confirmed, so although women using triptans can be
reassured, continued use during pregnancy is not
recommended unless no other treatment is effective.

Health care professionals are encouraged to report the
outcome of pregnancy in any women exposed to the
relevant safety databases (see Further Information). The
registries are based on observational, case registration and
follow-up studies designed to detect evidence of
teratogenicity associated with specific medications. Risk of
birth defects, as defined by the Centers for Disease Control
and Prevention, is compared with published risks both in
women in the general population and in women with the
underlying condition being treated, if available. Sumatriptan: Data from the large sumatriptan safety database
are reassuring and confirm that inadvertent exposure to
sumatriptan during pregnancy has not been associated with
adverse outcomes. The risk of first trimester birth defects in
the Sumatriptan Pregnancy Registry (1996 to 30 April 2006)
is 16/371 (i.e. 4.3%, 95% CI 2.6–7.1%). This compares
favourably with the 3–5% risk of birth defects in the general
population. However, although these data indicate that use
of sumatriptan in early pregnancy does not result in a large
increase in teratogenic risk, they do not rule out the possibility of a small increase in risk for a specific birth defect.

Table 3 Symptomatic drugs: use during pregnancy and lactation

<table>
<thead>
<tr>
<th>Drug</th>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen/paracetamol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Codeine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Aspirin</td>
<td>✓</td>
<td>✓</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>✓</td>
<td>✓</td>
<td>Avoid</td>
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</tr>
<tr>
<td>Ibuprofen</td>
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<td>Avoid</td>
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<td>Naproxen</td>
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<td>Prochlorperazine*</td>
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<td>Dihydroergotamine</td>
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CI, contraindicated; ID, insufficient data; IM, intramuscular; IV, intravenous; ?(✓), limited data but probably safe; ✓, data
suggest unlikely to cause harm; ✓, no evidence of harm; *, for emergency treatment of migraine not responding to standard measures.

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Shuhaiber et al. compared pregnancy outcome after exposure to sumatriptan with that of disease-matched controls and non-teratogen controls. There were no differences in the rates of live births, spontaneous miscarriages, therapeutic terminations or major birth defects among the three groups. This prospective study suggests that the use of sumatriptan during organogenesis is not associated with an apparent increased risk of major birth defects.42

O’Quinn et al. compared peripartum pregnancy outcomes in women who did and did not use subcutaneous sumatriptan after conception. This open-label, prospective study was conducted in 168 pregnancies that included 76 first trimester exposures to sumatriptan. There were no differences in pregnancy outcome between the two groups.44

Olesen et al. reviewed data from the Pharmaco-Epidemiological Prescription Database of North Jutland County regarding all women who had given birth in the county of North Jutland from 1991 to 1996. They identified 34 women exposed to sumatriptan during pregnancy. Using logistic regression models, their pregnancy outcome was compared with two groups of pregnant women: healthy women (n = 15,955) and migraine controls (n = 89), defined as migrating women who did not redeem prescription for migraine treatment during pregnancy. They found that the risk of preterm delivery was elevated among women exposed to sumatriptan compared with migraine controls (OR 6.3, 95% CI 1.2–32.0) and healthy women (OR 3.3, 95% CI 1.3–8.5). The risk of a low birth weight infant was increased (OR 3.0, 95% CI 1.3–7.0) for all migraine patients who delivered preterm (n = 115) compared with the outcome of healthy pregnancies.45 Although these findings could be due to drug exposure or disease severity, they have not been replicated in other studies.

A study of the Swedish Medical Birth Registry identified 658 women who had used sumatriptan and noted that the infants were more likely to be preterm and with a birth weight under 2500 g. However, this was non-significant. No other differences between those exposed to sumatriptan and women using other drugs for migraine during pregnancy were noted.46

Rizatriptan: Data from the rizatriptan Pregnancy Registry and reports from other sources do not suggest that treatment during pregnancy predisposes patients to spontaneous miscarriages or congenital anomalies above the normal rate. However, the number of reports is smaller. From June 1998 to 31 July 2006, 74 women have been enrolled in the Registry, 67 prospectively and seven retrospectively. Of the 67 prospective reports, 21 pregnancy outcomes are pending and 11 are unknown because the patients have been lost to follow-up. Of 30 live births, 28 were normal healthy term infants, one infant born at 35 weeks had hydrops, and one infant died at 24 weeks, attributed to an incompetent cervix. One late fetal death at approximately 37 weeks was attributed to a cord accident. One pregnancy ended in an elective termination at 21 weeks’ gestation following prenatal diagnosis of multiple anomalies due to partial replication of chromosome 3 attributed to advanced maternal age. Three spontaneous miscarriages under 12 weeks have been reported. Of the seven retrospective reports, three describe infants with congenital anomalies.

Specific prophylaxis for migraine in pregnancy

Non-drug prophylaxis

Non-drug therapies, such as relaxation, biofeedback and physical therapy, are safe and effective treatment alternatives for 80% of pregnant women.47 Further, the benefits are maintained beyond pregnancy.48

Drug prophylaxis (Table 4)

Low-dose aspirin

There has been one small trial involving 28 pregnant women with frequent or severe migraine attacks taking low-dose aspirin (75 mg) for migraine prophylaxis. There was no placebo control but 22 women reported subjective improvement.49 The authors base their rationale for using aspirin to prevent migraine on its ability to counteract the platelet activation that occurs in pregnancy. Low-dose aspirin has been extensively studied in pre-eclampsia during pregnancy with no increase in bleeding complications and negligible effects on the ductus arteriosus.

Beta-blockers

There is about a 25% risk of intrauterine growth retardation when atenolol is used at anti-hypertensive doses to treat essential hypertension in pregnancy.50 Other beta-blockers have not been systematically studied but it is generally assumed that this is a class effect, although a causative effect related to the underlying hypertension has not been ruled out. On this basis, if prophylaxis is considered necessary during pregnancy the lowest effective dose of propranolol or metoprolol are the drugs of choice. If beta-blockers are used in the third trimester, treatment should be stopped 2–3 days before delivery in order to reduce the likelihood of fetal bradycardia and a reduction in uterine contraction. Infants exposed to propranolol in utero should be monitored for hypoglycaemia.51

Antidepressants

There are conflicting data regarding limb deformities associated with use of amitriptyline during pregnancy, although these have been associated with high doses used for the management of depression. There are no reports associated with low doses between 10 and 50 mg at night used for pain management and migraine. Tachycardia, irritability, muscle spasms and convulsion have been reported in neonates of women taking antidepressive doses. Where clinically possible, it is recommended that the dose is tapered 3–4 weeks before delivery.

Anti-epileptics

Preliminary pregnancy registry information for topiramate shows no suggestion of fetal abnormalities or increased rate of miscarriage. Other anti-epileptic agents prescribed for migraine prophylaxis cannot justifiably be recommended during pregnancy. Sodium valproate, increasingly used for migraine prophylaxis, is contraindicated during pregnancy in the absence of epilepsy as there is a high risk of fetal abnormalities.52 Indeed, women prescribed sodium valproate for migraine must use effective contraception. Gabapentin, although safe for use in pregnancy, is considered at best to be a third-line prophylactic agent.39

Calcium channel blockers

Verapamil has limited efficacy and although it is generally considered safe, it is not recommended for migraine prophylaxis in pregnancy. Further, it has a tocolytic effect on the uterus, so should be avoided in late pregnancy.

Other drugs

Data for pizotifen are limited but there are no reports of adverse outcomes during pregnancy. Methysergide is contraindicated.

Many pregnant women use dietary supplements during pregnancy incorrectly assuming that because they are not

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'drugs' they must be safe. This belief is compounded by personnel in health food stores who are likely to ... ©FFPRHC J Fam Plann Reprod Health Care 2007: 33(2)
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MacGregor

larger sample sizes, are needed.55 If the woman has other harm and consider that more observational studies, with safety data rather than reports of actual fetal or maternal still have strong reservations based mainly on a lack of clear adverse effects on pregnancy outcomes. Some authorities experience significantly less nausea than women who do not containing vitamin B6 during the first 6 weeks of pregnancy multivitamins recommended in pregnancy with doses ranging from 10 to 25 mg. Women who take a multivitamin multivitamins vitamin B6 are neither necessary nor recommended.©FFPRHC J Fam Plann Reprod Health Care 2007: 33(2)
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Managing migraine during breastfeeding
Although recent studies suggest that the number of women choosing to breastfeed is rising, there is also evidence that women do not initiate breastfeeding or discontinue because of their concerns about taking medication.57 Unfortunately, many women and health care professionals rely on information in the package inserts, which may not be accurate. Maintaining breastfeeding during drug treatment is increasingly recommended. Headaches immediately postpartum can be severe, warranting effective treatment. Milk production on the first or second day postpartum is so low that the overall dose of any medication transferred is usually insignificant. In the following days drug exposure to the baby may be minimised if the mother takes medication immediately following breastfeeding or just before the baby is due a longer sleep period.

Acute drug treatment (Table 3)

Aspirin: is excreted in breast milk so breastfeeding mothers should avoid its use because of the theoretical risk of Reye’s syndrome and impaired platelet function in susceptible infants, although occasional use by the mother is unlikely to cause adverse effects.

Codeine: occasional use of over-the-counter drugs containing codeine is unlikely to cause harm, although large doses of codeine excreted in the breast milk can cause sedation and respiratory depression.

NSAIDs
The concentration of NSAIDs in breast milk is very low and is therefore unlikely to affect the infant.

Anti-emetics
There is no evidence to suggest that buclizine, chlorpromazine, cyclizine or prochlorperazine cannot be used during breastfeeding.

Domperidone, as well as being a prokinetic anti-emetic, is a dopamine agonist that stimulates prolactin. Since it does not cross the blood–brain barrier it is preferred to metoclopramide. Mean milk volume can increase by over 40% over 7 days. Milk levels of domperidone are minimal (only 1.2 ng/ml).

Metoclopramide increases milk production by up to 100% at doses of 10–15 mg three times a day. The amount of metoclopramide transferred into breast milk is small, ranging from 28 to 157 µg/l. The most significant adverse effects are extrapyramidal jerks and gastric cramping.

Ergots
Ergotamine and dihydroergotamine should not be used during breastfeeding as they inhibit lactation.

Triptans
The bioavailability of drugs and the amount of medication presented in milk throughout the day are two factors relevant to the safety of breastfeeding. Table 6 shows the oral bioavailability, $T_{1/2}$ and $T_{max}$ for the seven triptans. The most extensive triptan database is for sumatriptan.

The excretion of a 6 mg subcutaneous dose of sumatriptan in breast milk was studied in five subjects.58 The concentration in milk corresponded to an infant exposure of only 3.5% of the mother’s dose. The oral bioavailability is only 14% therefore the infant would only absorb 0.5% of the mother’s dose. Since sumatriptan is usually administered as a single dose at infrequent intervals, the low level of excretion in breast milk suggests that continued breastfeeding following its use would not pose a significant risk to the infant. Despite the Summary of Product Characteristics (SPC), at least one authority sanctions use of

<table>
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<td>Vitamin B6 (pyridoxine)</td>
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CI, contraindicated; ID, insufficient data; (?), limited data but probably safe; (Δ), data suggest unlikely to cause harm; v, no evidence of harm. ©FFPRHC J Fam Plann Reprod Health Care 2007: 33(2)
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sumatriptan during lactation. It should be noted that this recommendation is contrary to the SPC, which cautions that “Infant exposure can be minimised by avoiding breastfeeding for 12 hours after treatment, during which time any breast milk expressed should be discarded”.

The SPC for eletriptan states that in one study of eight women given a single 80 mg oral dose, the mean total amount of eletriptan in breast milk over 24 hours in this group was 0.02% of the dose. However, the SPC continues that “caution should be exercised when considering the administration of [eletriptan] to women who are breastfeeding. Infant exposure can be minimised by avoiding breastfeeding for 24 hours after treatment”.

Data on exposure during lactation are limited but the SPCs for almotriptan, frovatriptan and rizatriptan recommend avoiding breastfeeding for 24 hours after treatment. The SPCs for naratriptan and zolmitriptan SPCs state only that “caution should be exercised when considering administration of naratriptan to nursing women”.

Drug prophylaxis (Table 4)

Beta-blockers

Beta-blockers are not significantly excreted into breast milk and they can be used during breastfeeding. However, attention should be paid to the infant in case of bradycardia and hypoglycaemia. Propranolol or metoprolol are preferred to atenolol.

Antidepressants

Amitriptyline is detectable in breast milk but low doses used for migraine are unlikely to affect the infant adversely.

Anti-epileptics

The concentration of sodium valproate found in breast milk is very low so it can be used during breastfeeding. There are insufficient data to recommend gabapentin or topiramate.

Calcium channel blockers

There is no evidence of any risk associated with the use of verapamil during breastfeeding.

Other drugs

Safety of pizotifen during breastfeeding is not established, although concentrations in breast milk are not likely to adversely affect the infant. Methylsulfonyl is contraindicated.

Although supplemental doses of vitamin B2, vitamin B6 and co-enzyme Q10 are unlikely to affect the infant, high doses recommended for migraine prophylaxis should be avoided (Table 5).

Practical management recommendations

Analgesics and anti-emetics commonly used for the treatment of migraine can be continued throughout pregnancy. NSAIDs, particularly ibuprofen, can be taken in the first and second trimesters but should be avoided near term. Although a positive recommendation to use triptans during pregnancy cannot be made on the limited data available, women who have taken triptans can be reassured that their use is highly unlikely to result in any adverse outcome. Ergots are contraindicated. If there are no other risk factors involved, inadvertent exposure to any of the drugs used for the treatment of migraine, even those contraindicated for use during pregnancy, does not constitute medical grounds for termination of pregnancy.

When considering the need for prophylaxis during pregnancy, the natural history of improvement during the second and third trimesters should be borne in mind. Consequently, reassurance, identification and avoidance of relevant triggers, adequate hydration and regular meals, together with effective management of acute attacks, is often sufficient. The recommended prophylactic is propranolol. This drug has been widely used and there is no indication of an increased risk of malformations when it is used for migraine prevention during pregnancy. Ideally, the lowest effective dose should be used starting with 10–20 mg twice daily. Propranolol should be stopped 2–3 days before delivery in order to reduce the occurrence of slowed heart rate in the baby and a reduction in uterine contractions. The baby should be monitored for hypoglycaemia. Amitriptyline 10–50 mg at night can be used during the first and second trimester of pregnancy. A further alternative is topiramate. Otherwise healthy pregnant women can use small amounts of ginger to prevent nausea but should avoid high doses.

For symptomatic treatment of migraine when breastfeeding, an appropriate strategy is voltarol 50–100 mg by mouth or via the rectum, up to 200 mg per 24 hours, combined with domperidone 20 mg by mouth or 30–60 mg rectally up to four doses per 24 hours. Domperidone can promote the efficacy of analgesics by reversing gastric stasis in addition to treating nausea.

Sumatriptan can be used during breastfeeding. There is little reason why other triptans with low bioavailability and low absorption by the infant such as zolmitriptan, rizatriptan and eletriptan should not also be used. Even minor exposure could be largely avoided by expressing and discarding all milk for around 4 hours after dosing. Longer periods are not recommended as milk supply can reduce within 48 hours without full and repeated emptying of the breast.

For prophylaxis, propranolol in doses of 10–20 mg twice daily is a first-line strategy.

When recommending use of a drug in contradiction to the prescribing information in the SPC, the risks and benefits should be discussed with the woman, who may choose to use the drug on a named patient basis. The discussion should be documented in the notes.

What to do when nothing works

In the first instance the diagnosis should be reviewed, as this is the most likely reason for ineffective management. Medication overuse headache can also present during pregnancy and should be considered in any woman regularly taking symptomatic treatments for headache on more than 3 days a week, every week. This usually responds to immediate cessation of symptomatic treatment but may require supportive treatment. One option to consider in pregnancy is a 6-day reducing course of prednisolone: 60 mg/day for 2 days, 40 mg/day for 2 days and 20 mg/day for 2 days.

During pregnancy and breastfeeding, prochlorperazine 10 mg or chlorpromazine 25–50 mg by intramuscular injection are effective even without additional analgesia,
and together with intravenous fluids, are usually sufficient to abort an attack. Intravenous magnesium sulphate was well tolerated and effective in a randomised, single-blind, placebo-controlled trial of 30 patients. A combination of intravenous prochlorperazine 10 mg 8-hourly together with intravenous magnesium sulphate 1 g 12-hourly was used successfully to abort two cases of prolonged migraine aura during pregnancy.

Conclusions
Around 60–70% of women with migraine will improve in pregnancy, particularly during the second and third trimesters. Most medication is taken during the first trimester, which is the time of most concern for effects on organogenesis. Although therapeutic doses of most migraine treatments do not increase the risk of fetal malformation or miscarriage above the normal background rate, it is sensible to recommend the safest options. For acute treatment, paracetamol is safe throughout pregnancy. Aspirin and NSAIDs are also safe but are best avoided after 30 weeks. NSAIDs (but not aspirin) can be taken during lactation. Prochlorperazine and domperidone are preferred to metoclopramide but all can be used through pregnancy and lactation. Whilst prescription of triptans during pregnancy is not recommended, women inadvertently exposed to triptans during pregnancy can be reassured that there is evidence to support minimal, if any, risk. Sumatriptan can be taken during lactation. For continuing frequent attacks, which warrant prophylaxis, propranolol has best evidence of safety during pregnancy and lactation.

Statements on funding and competing interests
Funding None identified. Competing interests None identified.

FURTHER INFORMATION
The National Teratology Information Service (NTIS)
Regional Drug and Therapeutics Centre, Wolfson Unit, Claremont Place, Newcastle-upon-Tyne NE2 4HH, UK. Monday–Friday (office hours). Tel: +44 (0) 191 232 1525. Fax: +44 (0) 191 260 6193. Monday–Friday (1700–2000 for urgent enquiries). Tel: +44 (0) 191 282 5944. NTIS is funded by the Department of Health to provide a national service on all aspects of toxicity of drugs and chemicals in pregnancy throughout the UK.

Sumatriptan and Naratriptan Pregnancy Registry
http://pregnANCyregisTry.gsk.com
Health care providers can obtain interim registry results and register patients by telephoning the Registry project office directly at +1 800 336 2176 (toll-free in the USA) or +1 910 256 0549 or by completing the appropriate enrolment form by clicking on the registry name shown below and either returning the form to the registry by fax at +1 800 800 1052 or +1 910 256 0637 or by mail to: Sumatriptan and Naratriptan Pregnancy Registry, Registries and Epidemiology, Kendle International Inc., Research Park, 1011 Ashes Drive, Wilmington, NC 28405, USA.

Merck Pregnancy Registry Program (Rizatriptan)
http://www.merckpregnANCyregistries.com/maxalt.html
Merck & Company, Inc., Merck National Service Center. Phone: +1 800 986 8999 (toll-free in the USA). Fax: +1 484 344 2328.

For information on drugs in pregnancy and breastfeeding
American Academy of Pediatrics: http://www.pediatrics.org/cgi/content/full/108/3/776


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