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.[1] Although migraine without aura accounts for the majority of migraine, particularly in women, the overall 1-year prevalence of migraine with aura is around 5% for women and 2% for men.[1] 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.[1] 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.[2] 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 women taking an average of four to five different medications.[3] 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 folic 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.[4,5]

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.[6]

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.[7]

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.[8–10]

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.[9] Women with pre-existing migraine without aura may develop aura for the first time during pregnancy.[11,12] Also, if a woman has her first ever migraine when pregnant, it is likely to be with aura.[13,14]

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).[11,15,16] 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.[17] They evaluated 22 843 newborns or fetuses with congenital abnormalities, 38 151 control newborn infants without any abnormalities and 834 controls with Down syndrome. Migraine during

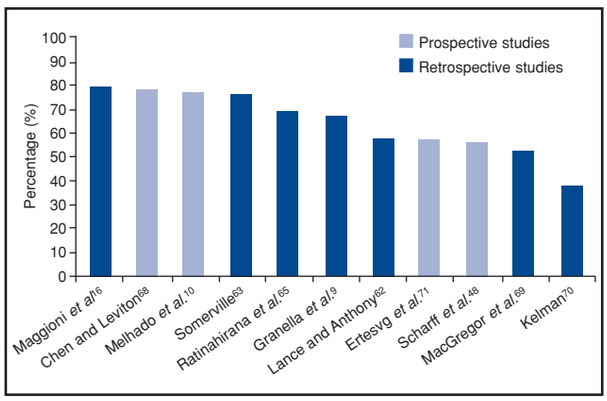

Figure 1 Percentage of women reporting improvement in pregnancy

J Fam Plann Reprod Health Care 2007; **33**(2): 83–93
(Accepted 25 January 2007)

The City of London Migraine Clinic, London, UK and Barts Sexual Health, St Bartholomew's Hospital, London, UK
E Anne MacGregor, MFFP, *Director of Clinical Research*

Correspondence to: Dr Anne MacGregor, The City of London Migraine Clinic, 22 Charterhouse Square, London EC1M 6DX, UK. E-mail: anne.macgregor@sinoragram.co.uk

Table 1 Effect of pregnancy on migraine

Study	Study design	Sample size	Outcome				Comments
			Improvement or complete remission	Unchanged	Worsened	New onset	
Lance and Anthony (1966)[62]	Retrospective	120 women with pre-existing migraine/252 pregnancies	58%	42%		NA	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
Somerville (1972)[63]	Retrospective	38 women with migraine during pregnancy	63% (18.5% complete remission)	18.5%		18.5%	
Manzoni *et al.* (1986)[64]	Retrospective	74 women with migraine who had at least one pregnancy: 36 MO, 38 MA	NR	16.1% MO 40% MA (p<0.05)		2.8% MO 25.7% MA (p<0.05)	
Ratinahirana *et al.* (1990)[65]	Retrospective survey 1–3 days postpartum	703 women 116 with migraine: 90 MO, 26 MA	69.4%	7.5%	6.8%	10.9%	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)
Rasmussen and Olesen (1992)[66]	Retrospective	1000 people of which those who had been pregnant: 21 MA, number not stated MO	53% MO 33% MA	43% MO 62% MA	4% MO 5% MA	NR	
Granella *et al.* (1993)[67]	Retrospective	1300 women with migraine; 571 with migraine before first pregnancy	67.3% (17.4% complete remission)	29.2%	3.5%	1.3%	Remission more frequent, in women with MM (10/44 cases, 22.7%) compared to women suffering from random attacks (39/232 cases, 16.8%) (NS) In MM sufferers, onset or worsening of headache never occurred during pregnancy, as opposed to the non-MM group (2/232 and 11/232, respectively)
Chen and Leviton (1994)[68]	Prospective observational study	484 women with migraine at prenatal visit	79%: 17% complete remission throughout pregnancy; 62% ≥2 attacks in third trimester	21%	NR	NA	47% of women who had migraine without preceding or accompanying visual disturbance improved during pregnancy vs 28% of women who had migraine preceded/accompanied by visual disturbances
Cupini *et al.* (1995)[13]	Comparative study	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	MO 30.7% MA 20%	MO 55% MA 53.3%	MO 3.8% MA 6.6%	MO 0% MA 5.2%	Migraine began during pregnancy in a significantly higher percentage of MA than of MO patients (p<0.01) Improvement or disappearance of migraine was significantly more frequent than worsening of migraine in both MO and MA (p<0.0001 and p<0.005, respectively). Improvement of migraine during pregnancy was more common in patients who reported a relationship between migraine and menses than in all other patients (p<0.05) Postpartum 6.8% MO vs 0% MA (NS)

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 1 Effect of pregnancy on migraine (continued)

Study	Study design	Sample size	Outcome				Comments
			Improvement or complete remission	Unchanged	Worsened	New onset	
MacGregor *et al.* (1997)[69]	Retrospective questionnaire	100 women; 30 with migraine before first pregnancy	53%	27%	0	1 MO	20% could not recall effects of pregnancy on migraine
Scharff *et al.* (1997)[26]	Prospective diary	30 women with headaches ≥2 per month	56.7% (NS)	36.7%	6.7%	NA	Headache recorded daily throughout pregnancy and up to 12/52 postpartum Improvement = change score of ≥50 Trend for headache to increase during the birth week (NS)
Maggioni *et al.* (1997)[16]	Retrospective questionnaire	430 women 3 days postpartum 81 MO, 12 MA, 33 TH	In all three groups: 80% had ≥50% headache reduction Improvement was more evident after the end of the first trimester	NR	NR	1 case of new onset MO	
Marcus *et al.* (1999)[7]	Longitudinal prospective	49 women: 16 M; 16 TH; 15 M+TH	30% improvement between second and third trimesters (NS)	NR	NR	NR	Headache recorded daily throughout pregnancy and 3/12 postpartum
Granella *et al.* (2000)[9]	Retrospective case control	100 MA; 200 MO controls	MO 76.8% MA 43.6% OR 0.2 (95% CI 0.1–0.5)	NR	NR	NR	
Sances *et al.* (2003)[8]	Prospective diary	49 women with migraine during 3/12 before pregnancy: 47 MO; 2 MA	MO first trimester 46.8% (10.6% complete remission) MO second trimester 83.0% (53.2% complete remission) Third trimester 87.2% (78.7% complete remission)	MO 23% MA 100%		NA	Return of migraine: first week postpartum 34.0%; first month postpartum 55.3% Breastfeeding protected against migraine
Kelman (2004)[70]	Retrospective questionnaire	504 women with migraine: 61.3% had had a pregnancy	38.2% (20.4% complete remission)	27.8%	34%	NA	Patients with 100% aura were significantly different from patients with 0% aura, being more likely to have headaches occurring during pregnancy ($p<0.05$)
Melhado *et al.* (2005)[10]	Prospective cohort	993 pregnant women with headaches prior to gestation 332 women reported MM; 516 reported non-MM	Of women with MM, 62% during the first trimester; 74% during the second trimester; 78% during the third trimester	NR	NR	NA	Women who suffered from non-menstrual headaches improved during pregnancy but not as much as women with menstrual headaches
Ertresvag *et al.* (2005)[71]	Prospective questionnaire	1631 pregnant women	58%	NR	NR	1.9%	Transient neurological symptoms were less common among individuals without or with non-migrainous headache compared with migraine. This may indicate that there is an increased susceptibility of unknown cause for these symptoms among migraine patients during pregnancy

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 [crude prevalence odds ratio (POR) 1.3, 95% CI 1.2–1.5] and 24 (2.9%) pregnant women in the Down syndrome control group (crude POR 0.9, 95% CI 0.6–1.3). Of all the parameters studied, the only positive finding was that limb deficiencies were associated with a higher rate of maternal migraines 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.[18–23] 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).[24] 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.[8,25,26] 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.[27] 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).[28] 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.[7] 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 ($p = 0.0003$).[8]

Pathophysiology

Fluctuations in estrogen levels, particularly declining levels after a stable estrogen state, are known to increase migraine in some susceptible women.[29,30] 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.[31] 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.[32] Other relevant effects of the pregnant state include increased muscle relaxation and reduced hypoglycaemic response.

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.[33] Pregnancy is associated with varying degrees of platelet hyperaggregation, although opposing haemostatic changes attenuate this effect in most, but not all, women.[34] Platelet hyperaggregation might also account for the increased risk of ischaemic stroke associated with migraine with aura and the development of pre-eclampsia in pregnancy.[35]

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.[36] 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 2 Effect of migraine on pregnancy

Study	Study design	Sample size	Outcome	Worsened	Comments
Wainscott *et al.* (1978)[15]	Case control	777 women with migraine vs 183 controls	Miscarriage, stillbirth, toxaemia of pregnancy, congenital malformations	No difference between migraineurs and controls	Similar outcome to national average Suggests neither migraine nor drugs commonly used for migraine affect outcome
Moore and Redman (1983)[19]	Case control	24 women with severe eclampsia <34/40 vs 48 age and parity matched controls	Migraine as a risk factor for early onset pre-eclampsia	Migraine associated with increased risk of pre-eclampsia	
Marcoux *et al.* (1992)[20]	Case control	426 cases (172 pre-eclampsia; 254 gestational hypertension) vs 505 controls	Likelihood of migraine in the year before pregnancy in cases vs controls	Migraine associated with increased risk of pre-eclampsia: OR 2.44 (95% CI 1.42–4.20) Migraine associated with increased risk of gestational hypertension: OR 1.70 (95% CI 1.02–2.85)	
Olesen *et al.* (2000)[45]	Case control	115 pregnant women with migraine vs healthy pregnant controls	Risk of preterm delivery and low birth weight	Risk of low birth weight was increased: OR 3.0 (95% CI 1.3–7.0) for migraineurs who delivered at term vs controls	
Facchinetti *et al.* (2005)[21]	Case control	75 cases with recent pre-eclampsia vs 75 controls with uneventful pregnancy at term	Headache in cases vs controls	Headache in 47/75 with pre-eclampsia vs 19/75 controls OR 4.95 (95% CI 2.47–9.92)	
Adeney *et al.* (2005)[24]	Case control	244 cases with pre-eclampsia vs 470 normotensive controls	Risk of pre-eclampsia	Migraine associated with increased risk of pre-eclampsia OR 1.8 (95% CI 1.1–2.7)	
Banhidy *et al.* (2006)[17,23]	Case control	22 843 cases with congenital abnormalities vs 38 151 normal controls and 834 controls with Down syndrome (malformed control)	Prevalence of severe migraine during pregnancy in the mothers	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	
			Risk of pre-eclampsia in mothers of normal controls and mean gestational age and birth weight in normal controls born to mothers with or without migraine	Severe migraine associated with increased risk of pre-eclampsia and severe nausea/vomiting No difference in proportion of low birth weight and preterm births	
			Rate of migraine in mothers of cases with congenital abnormalities vs controls	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 control 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	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
James *et al.* (2005)[28]	Observational study	2850 pregnancy-related strokes from the Nationwide Inpatient Sample 2000–2001	Incidence and risk factors for stroke in pregnancy and the puerperium	Stroke rate 34.2 per 100 000 deliveries Migraine OR 16.9 (95% CI 9.7–29.5)	Migraine has not previously been reported as a risk factor for pregnancy-related stroke. Risk associated with migraine was greater than with other risk factors

CI, confidence interval; OR, odds ratio; POR, prevalence odds ratio.

Table 3 Symptomatic drugs: use during pregnancy and lactation[37,57,72]

Drug	First trimester	Second trimester	Third trimester	Lactation
Acetaminophen/ paracetamol	✓	✓	✓	✓
Codeine	(✓)	(✓)	(✓)	✓
Aspirin	(✓)	(✓)	Avoid	Avoid
Diclofenac	(✓)	(✓)	Avoid	✓
Ibuprofen	(✓)	(✓)	Avoid	✓
Naproxen	(✓)	(✓)	Avoid	✓
Buclizine	(✓)	(✓)	(✓)	✓
Cyclizine	(✓)	(✓)	(✓)	✓
Domperidone	(✓)	(✓)	(✓)	✓
Doxylamine	(✓)	(✓)	(✓)	(✓)
Metoclopramide	(✓)	(✓)	(✓)	(✓)
Prochlorperazine*	(✓)	(✓)	(✓)	✓
Dihydroergotamine	CI	CI	CI	CI
Ergotamine	CI	CI	CI	CI
Almotriptan	ID	ID	ID	ID
Eletriptan	ID	ID	ID	(✓)
Frovatriptan	ID	ID	ID	ID
Naratriptan	?(✓)	?(✓)	?(✓)	(✓)
Rizatriptan	?(✓)	?(✓)	?(✓)	(✓)
Sumatriptan	?(✓)	?(✓)	?(✓)	✓
Zolmitriptan	ID	ID	ID	(✓)
Chlorpromazine IM*	(✓)	(✓)	(✓)	✓
Magnesium sulphate IV*	(✓)	(✓)	(✓)	(✓)
Prednisolone*	(✓)	(✓)	(✓)	(✓)

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.

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.[37]

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.[38] 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.[39] 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.[40] 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.[37]

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.[41]

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.[42]

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.

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.[43]

O'Quinn *et al*. compared perinatal 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 migraine patients who did not redeem prescriptions 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 at term ($n = 115$) 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 small. 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 hypospadias, 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.

Other triptans: There are insufficient data on other triptans.

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

Table 4 Prophylactic drugs: use during pregnancy and lactation[37,57,72]

Drug	First trimester	Second trimester	Third trimester	Lactation
Amitriptyline	(✓)	(✓)	(✓)	(✓)
Low-dose aspirin	(✓)	(✓)	Avoid	Avoid
Atenolol	Avoid	Avoid	Avoid	(✓)
Gabapentin	?(✓)	?(✓)	?(✓)	ID
Methysergide	CI	CI	CI	CI
Metoprolol	(✓)	(✓)	(✓)	✓
Pizotifen	ID	ID	ID	ID
Propanolol	(✓)	(✓)	(✓)	✓
Topiramate	ID	(✓)	(✓)	ID
Valproate	CI	ID	ID	✓
Verapamil	(✓)	(✓)	Avoid	✓

CI, contraindicated; ID, insufficient data; ?(✓), limited data but probably safe; (✓), data suggest unlikely to cause harm; ✓, no evidence of harm.

'drugs' they must be safe. This belief is compounded by personnel in health food stores who are likely to give inadequate or even incorrect advice about the safety of these products.[53,54] Having a reasonable knowledge of the efficacy and safety of some of the commonly used herbs and vitamins is useful when counselling pregnant women (Table 5).

Ginger is often used for morning sickness during the first trimester of pregnancy. In extensive reviews of studies using ginger as an agent to reduce morning sickness, several authors have concluded that ginger, in doses of around 1 g daily, may be beneficial. A recent review of six double-blind randomised controlled trials with a total of 675 participants and a prospective observational cohort study (n = 187) showed efficacy in the absence of significant side effects or adverse effects on pregnancy outcomes. Some authorities still have strong reservations based mainly on a lack of clear safety data rather than reports of actual fetal or maternal harm and consider that more observational studies, with larger sample sizes, are needed.[55] If the woman has other medical conditions or is taking medication it is advisable for her to consult her general practitioner before using ginger to minimise the development of possible adverse effects.[37]

Vitamin B6 (pyridoxine) is included in most multivitamins recommended in pregnancy with doses ranging from 10 to 25 mg. Women who take a multivitamin containing vitamin B6 during the first 6 weeks of pregnancy experience significantly less nausea than women who do not take a multivitamin.[56] As with most vitamins, megadoses of vitamin B6 are neither necessary nor recommended.

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.

Table 5 Herbs/vitamins for migraine: use during pregnancy and lactation[37,55]

Drug	First trimester	Second trimester	Third trimester	Lactation
Vitamin B2 (riboflavin)	✓*	✓*	✓*	✓*
Vitamin B6 (pyridoxine)	✓*	✓*	✓*	✓*
Coenzyme Q10	ID	ID	ID	✓*
Feverfew	CI	CI	CI	CI
Butterbur	ID	ID	ID	ID
Ginger	(✓)*	(✓)*	(✓)*	(✓)*

CI, contraindicated; ID, insufficient data; ?(✓), limited data but probably safe; (✓), data suggest unlikely to cause harm; ✓, no evidence of harm; ✓*, avoid megadoses.

Acute drug treatment (Table 3)

Analgesics

Acetaminophen/paracetamol is the analgesic of choice during breastfeeding.

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 bioavailabilty, $T_{1/2}$ 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 6 Triptan pharmacokinetics

Parameter	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan
Oral bioavailability (%)	69	50	24–30	63–74	40	14	40
$T_{1/2}$ (hours)	3.5	5	25	5–6.3	2	2	3
T_{max} (hours)	2–3	1.5–3	3	2–3	1	2–2.5	2–4

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 *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. *Methysergide* 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.[39] 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.[59]

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.[60] 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.[61]

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

References

1 Rasmussen BK, Jensen R, Schroll M, Olesen J. Epidemiology of headache in a general population – a prevalence study. *J Clin Epidemiol* 1991; **44**: 1147–1157.
2 Higgins J, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions 4.2.6* (updated September 2006). Chichester, UK: John Wiley & Sons, 2006.
3 Bonati M, Bortolus R, Marchetti F, Romero M, Tognoni G. Drug use in pregnancy: an overview of epidemiological (drug utilization) studies. *Eur J Clin Pharmacol* 1990; **38**: 325–328.
4 Ashkenazi J, Goldman JA, Dicker D, Feldberg D, Goldman GA. Adverse neurological symptoms after gonadotropin-releasing hormone analog therapy for in vitro fertilization cycles. *Fertil Steril* 1990; **53**: 738–740.
5 Amir BY, Yaacov B, Guy B, Gad P, Itzhak W, Gal I. Headaches in women undergoing *in vitro* fertilization and embryo-transfer treatment. *Headache* 2005; **45**: 215–219.
6 Aromaa M, Rautava P, Helenius H, Sillanpää ML. Prepregnancy headache and the well-being of mother and newborn. *Headache* 1996; **36**: 409–415.
7 Marcus DA, Scharff L, Turk D. Longitudinal prospective study of headache during pregnancy and postpartum. *Headache* 1999; **39**: 625–632.
8 Sances G, Granella F, Nappi RE, Fignon A, Ghiotto N, Polatti F, *et al.* Course of migraine during pregnancy and postpartum: a prospective study. *Cephalalgia* 2003; **23**: 197–205.
9 Granella F, Sances G, Pucci E, Nappi RE, Ghiotto N, Napp G. Migraine with aura and reproductive life events: a case control study. *Cephalalgia* 2000; **20**: 701–707.
10 Melhado E, Maciel JA Jr, Guerreiro CA. Headaches during pregnancy in women with a prior history of menstrual headaches. *Arq Neuropsiquiatr* 2005; **63**: 934–940.
11 Wright G, Patel M. Focal migraine and pregnancy. *BMJ* 1986; **293**: 1557–1558.
12 Chancellor AM, Wroe SJ, Cull RE. Migraine occurring for the first time in pregnancy. *Headache* 1990; **30**: 224–227.
13 Cupini LM, Matteis M, Troisi E, Calabresi P, Bernardi G, Silvestrini M. Sex-hormone-related events in migrainous females. A clinical comparative study between migraine with aura and migraine without aura. *Cephalalgia* 1995; **15**: 140–144.
14 Mandel S. Hemiplegic migraine in pregnancy. *Headache* 1988; **28**: 414–416.
15 Wainscott G, Sullivan M, Volans G, Wilkinson M. The outcome of pregnancy in women suffering from migraine. *Postgrad Med* 1978; **54**: 98–102.
16 Maggioni F, Alessi C, Maggino T, Zanchin G. Headache during pregnancy. *Cephalalgia* 1997; **17**: 765–769.
17 Banhidy F, Acs N, Horvath-Puho E, Czeizel AE. Maternal severe migraine and risk of congenital limb deficiencies. *Birth Defects Res A Clin Mol Teratol* 2006; **76**: 592–601.
18 Rotton WN, Sachtleben MR, Friedman EA. Migraine and eclampsia. *Obstet Gynecol* 1959; **14**: 332–330.
19 Moore MP, Redman CW. Case-control study of severe pre-eclampsia of early onset. *BMJ* 1983; **287**: 580–583.
20 Marcoux S, Berube S, Brisson J, Fabia J. History of migraine and risk of pregnancy-induced hypertension. *Epidemiology* 1992; **3**: 53–56.
21 Facchinetti F, Allais G, D'Amico R, Benedetto C, Volpe A. The relationship between headache and preeclampsia: a case-control study. *Eur J Obstet Gynecol Reprod Biol* 2005; **121**: 143–148.
22 Scher AI, Terwindt GM, Picavet HS, Verschuren WM, Ferrari MD, Launer LJ. Cardiovascular risk factors and migraine: the GEM population-based study. *Neurology* 2005; **64**: 614–620.
23 Banhidy F, Acs N, Horvath-Puho E, Czeizel AE. Pregnancy complications and delivery outcomes in pregnant women with severe migraine. *Eur J Obstet Gynecol Reprod Biol* 2006 [Epub 8 November 2006].
24 Adeney KL, Williams MA, Miller RS, Frederick IO, Sorensen TK, Luthy DA. Risk of preeclampsia in relation to maternal history of migraine headaches. *J Matern Fetal Neonatal Med* 2005; **18**: 167–172.
25 Stein G, Morton J, Marsh A, Collins W, Branch C, Desaga U, et al. Headaches after childbirth. *Acta Neurol Scand* 1984; **69**: 74–79.
26 Scharff L, Marcus DA, Turk DC. Headache during pregnancy and in the postpartum: a prospective study. *Headache* 1997; **37**: 203–210.
27 Kittner SJ, Stern BJ, Feeser BR, Hebel R, Nagey DA, Buchholz DW, *et al.* Pregnancy and the risk of stroke. *N Engl J Med* 1996; **335**: 768–774.
28 James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol* 2005; **106**: 509–516.

29 MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. *Neurology* 2006; **67**: 2154–2158.
30 MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Prevention of menstrual attacks of migraine: a double-blind placebo-controlled crossover study. *Neurology* 2006; **67**: 2159–2163.
31 Campbell OM, Gray RH. Characteristics and determinants of postpartum ovarian function in women in the United States. *Am J Obstet Gynecol* 1993; **169**: 55–60.
32 Dawson-Basoa MB, Gintzler AR. 17-Beta-estradiol and progesterone modulate an intrinsic opioid analgesic system. *Brain Res* 1993; **601**: 241–245.
33 Hanington E. Migraine is a platelet disorder. *Headache* 1987; **27**: 401–402.
34 Bonnar AJ, NcNicol GP, Douglas AS. Coagulation and fibrinolytic mechanisms during and after normal childbirth. *BMJ* 1970; **2**: 200–203.
35 Redman CW, Bonnar J, Beilin LJ. Early platelet consumption in pre-eclampsia. *BMJ* 1978; **1**: 467–469.
36 Amery WK, Vandenbergh V. What can precipitating factors teach us about the pathogenesis of migraine? *Headache* 1987; **27**: 146–150.
37 The National Teratology Information Service. http://www.spib.axl.co.uk [Accessed 25 December 2006].
38 Slone D, Siskind V, Heinonen OP, Monson RR, Kaufman DW, Shapiro S. Aspirin and congenital malformation. *Lancet* 1976; **1**: 1373–1375.
39 Steiner TJ, MacGregor EA, Davies PTG. *Guidelines for All Doctors in the Diagnosis and Management of Migraine and Tension-Type Headache* (2nd edn) (British Association for the Study of Headache Management Guidelines). 2004. http://64.227.208.149/NS_BASH/BASH_guidelines_1Feb06.pdf [Accessed 25 December 2006].
40 Byron M. Treatment of rheumatic diseases. In: Rubin P (ed.), *Prescribing in Pregnancy* (3rd edn). London, UK: BMJ Books, 2000; 87–100.
41 Czeizel AE. Teratogenicity of ergotamine. *J Med Genet* 1989; **26**: 69–70.
42 Reiff-Eldridge R, Heffner CR, Ephross SA, Tennis PS, White AD, Andrews EB. Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: a pharmaceutical company commitment. *Am J Obstet Gynecol* 2000; **182**: 159–163.
43 Shuhaiber S, Pastuszak A, Schick B, Matsui D, Spivey G, Brochu J, *et al.* Pregnancy outcome following first trimester exposure to sumatriptan. *Neurology* 1998; **51**: 581–583.
44 O'Quinn S, Ephross SA, Williams V, Davis RL, Gutterman DL, Fox AW. Pregnancy and perinatal outcomes in migraineurs using sumatriptan: a prospective study. *Arch Gynecol Obstet* 1999; **263**: 7–12.
45 Olesen C, Steffensen FH, Sorensen HT, Nielsen GL, Olsen J. Pregnancy outcome following prescription for sumatriptan. *Headache* 2000; **40**: 20–24.
46 Kallen B, Lygner P. Delivery outcome in women who used drugs for migraine during pregnancy with special reference to sumatriptan. *Headache* 2001; **41**: 351–356.
47 Marcus DA, Scharff L, Turk DC. Nonpharmacological management of headaches during pregnancy. *Psychosom Med* 1995; **57**: 527–535.
48 Scharff L, Marcus DA, Turk DC. Maintenance of effects in the nonmedical treatment of headaches during pregnancy. *Headache* 1996; **36**: 285–290.
49 Nelson-Piercy C, De Swiet M. Diagnosis and management of migraine. Low dose aspirin may be used for prophylaxis. *BMJ* 1996; **313**: 691–692.
50 Butters L, Kennedy S, Rubin P. Atenolol in essential hypertension during pregnancy. *BMJ* 1990; **301**: 587–589.
51 Habib A, McCarthy JS. Effects on the neonate of propranolol administered during pregnancy. *J Pediatr* 1977; **91**: 808–811.
52 Lindhout D, Schmidt D. *In utero* exposure to valproate and neural tube defects. *Lancet* 1986; **1**: 1392–1393.
53 Buckner KD, Chavez ML, Raney EC, Stoehr JD. Health food stores' recommendations for nausea and migraines during pregnancy. *Ann Pharmacother* 2005; **39**: 274–279.
54 Marcus DM, Snodgrass WR. Do no harm: avoidance of herbal medicines during pregnancy. *Obstet Gynecol* 2005; **105**(5 Pt 1): 1119–1122.
55 Borrelli F, Capasso R, Aviello G, Pittler MH, Izzo AA. Effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting. *Obstet Gynecol* 2005; **105**: 849–856.
56 Emelianova S, Mazzotto P, Einarson A, Koren G. Prevalence and severity of nausea and vomiting of pregnancy and effect of vitamin supplementation. *Clin Invest Med* 1999; **22**: 106–110.
57 Ahluwalia IB, Morrow B, Hsia J. Why do women stop breastfeeding? Findings from the Pregnancy Risk Assessment and Monitoring System. *Pediatrics* 2005; **116**: 1408–1412.
58 Wojnar-Horton RE, Hackett LP, Yapp P, Dusci LJ, Paech M, Ilett KF. Distribution and excretion of sumatriptan in human milk. *Br J Clin Pharmacol* 1996; **41**: 217–221.
59 Krymchantowski AV, Barbosa JS. Prednisone as initial treatment of analgesic-induced daily headache. *Cephalalgia* 2000; **20**: 107–113.
60 Demirkaya S, Vural O, Dora B, Topcuoglu MA. Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. *Headache* 2001; **41**: 171–177.
61 Rozen TD. Aborting a prolonged migrainous aura with intravenous prochlorperazine and magnesium sulfate. *Headache* 2003; **43**: 901–903.
62 Lance J, Anthony M. Some clinical aspects of migraine. *Arch Neurol* 1966; **15**: 356–361.
63 Somerville BW. A study of migraine in pregnancy. *Neurology* 1972; **22**: 824–828.
64 Manzoni GC, Farina S, Granella F, Alfieri M, Bisi M. Classic and common migraine suggestive clinical evidence of two separate entities. *Funct Neurol* 1986; **1**: 112–122.
65 Ratinahirana H, Darbois Y, Bousser M-G. Migraine and pregnancy: a prospective study in 703 women after delivery. *Neurology* 1990; **40**(Suppl. 1): 437.
66 Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. *Cephalalgia* 1992; **12**: 221–228.
67 Granella F, Sances G, Zanferrari C, Costa A, Martignoni E, Manzoni GC. Migraine without aura and reproductive life events: a clinical epidemiological study in 1300 women. *Headache* 1993; **33**: 385–389.
68 Chen T-C, Leviton A. Headache recurrence in pregnant women with migraine. *Headache* 1994; **34**: 107–110.
69 MacGregor EA, Igarashi H, Wilkinson M. Headaches and hormones: subjective versus objective assessment. *Headache Quarterly* 1997; **8**: 126–136.
70 Kelman L. Women's issues of migraine in tertiary care. *Headache* 2004; **44**: 2–7.
71 Ertresvag JM, Zwart JA, Helde G, Johnsen HJ, Bovim G. Headache and transient focal neurological symptoms during pregnancy, a prospective cohort. *Acta Neurol Scand* 2005; **111**: 233–237.
72 http://www.perinatology.com/exposures/druglist.htm [Accessed 30 December 2006].

READERS' CONTRIBUTIONS INVITED ON 'A BETTER WAY OF WORKING'

Continuing in this issue (see article on page 78) is the feature entitled 'A Better Way of Working', the purpose of which is to disseminate service delivery suggestions likely to be of interest and relevance to the Journal's readership.

Readers are invited to submit suggestions based on their own personal experience for consideration by the Journal Editor. Contributions should not exceed 250–500 words and should be written in a standardised format responding to the following four questions (or similar): Why was change needed? How did you go about implementing change? What advice would you give to others who might be considering a similar course of action? How did you show that the change had occurred?

All contributions should be submitted via the Journal's online submission system at **http://jfprhc.allentrack.net.**