

Pharmacological treatment of migraine during pregnancy and breastfeeding

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Abstract | Migraine affects up to 25% of women of reproductive age. In the majority of these women, migraine improves progressively during pregnancy, but symptoms generally recur shortly after delivery. As suboptimally treated migraine in pregnancy could have negative consequences for both mother and fetus, the primary aim of clinicians should be to provide optimal treatment according to stage of pregnancy, while minimising possible risks related to drug therapy. Nonpharmacological approaches are always first-line treatment, and should also be used to complement any required drug treatment. Paracetamol is the preferred drug for acute treatment throughout pregnancy. If paracetamol is not sufficiently effective, sporadic use of sumatriptan can be considered. NSAIDs such as ibuprofen can also be used under certain circumstances, though their intake in the first and third trimesters is associated with specific risks and contraindications. Preventive treatment should only be considered in the most severe cases. In women contemplating pregnancy, counselling is essential to promote a safe and healthy pregnancy and postpartum period for the mother and child, and should involve a dialogue addressing maternal concerns and expectations about drug treatment. This Review summarizes current evidence of the safety of the most common antimigraine medications during pregnancy and breastfeeding, and provides treatment recommendations for use in clinical practice.

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Introduction

Migraine is common among women of reproductive age, peaking in the fourth decade of life with a one-year prevalence of about 25%.^{1,2} Hormonal fluctuations in connection with menarche, menstruation cycle, pregnancy, menopause, use of oral contraceptives, and hormonal replacement therapy are known to influence attack frequency and severity.³

Up to 80–90% of women with migraine experience a progressive improvement of symptoms during pregnancy, and some even experience complete remission.^{4,5} Spontaneous remission is less common in patients with migraine with aura or migraine unrelated to the menstrual cycle.⁶ Of women with any type of migraine, 4–8% get worse during pregnancy,⁷ and in a few individuals, migraine appears for the first time during gestation, usually in the first trimester.⁸ In more than half of women who experience improvement during pregnancy, migraine will return to the level that preceded pregnancy within a month after delivery.^{4,9} In addition, the puerperium is often associated with factors that can trigger or exacerbate migraine, such as sleep deprivation and stress. There is somewhat conflicting evidence as to whether breastfeeding protects from recurrence of migraine after delivery.¹⁰

Nonpharmacological preventive approaches, including avoidance of triggering and exacerbating factors, ensuring

adequate nutrition and sleep, exercise, biofeedback and relaxation are safe and potentially effective strategies that should be tried as first-line treatment during pregnancy.¹¹ When an attack is imminent, measures such as bed-rest in a quiet, dark room, or some hours of sleep may help to relieve symptoms and possibly reduce the need for medication.

Although medication use in general should be limited while pregnant or breastfeeding, many women suffer from serious and debilitating migraine attacks that are not sufficiently controlled by nonpharmacological strategies alone. In a cohort study of 3,480 women with migraine during pregnancy, more than 70% reported using antimigraine drugs, most frequently non-narcotic analgesics (54%) and triptans (25%).¹² Medication use is even higher among breastfeeding women with migraine.¹⁰

Suboptimally treated migraine during pregnancy can have negative consequences for the mother and the fetus, including impaired nutrition, dehydration, sleep deprivation, increased stress, and depression.¹³ Moreover, several studies have suggested associations between active migraine during pregnancy and an increased risk of vascular complications, including stroke, gestational hypertension, and pre-eclampsia.^{14–17} Pregnant women with severe gestational hypertension or pre-eclampsia are at a higher risk of preterm delivery, giving birth to small-for-gestational-age newborns, and placental abruption.¹⁸ Thus, providing adequate migraine treatment is imperative not only for maternal benefit, but also for fetal and neonatal health.

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Key points

- Migraine affects up to one in four women of reproductive age, but migraine will often improve spontaneously during pregnancy
- Nonpharmacological approaches should always be tried as first-line treatment for migraine during pregnancy
- Several effective acute antimigraine medications are reasonably safe to use for pregnant and breastfeeding women
- In pregnancy, preventive drug therapy should be considered only in the most severe migraine cases
- Periconceptional counselling is important to promote a safe and healthy pregnancy and postpartum period for the mother and child

Management of migraine with medications during pregnancy and in the postpartum period is challenging because of the potential risks to the fetus and infant. Many of the commonly used drugs against migraine lack documentation of safety related to exposure *in utero* or via breast milk. Modifications of established therapeutic regimens could thus be necessary to find safer therapeutic options. Decisions about treatment should always be based on a thorough and individual risk–benefit evaluation to provide effective treatment that ensures maternal health and well-being while minimising potential adverse effects in the fetus and nursing infant.

This article aims to summarize current evidence about acute and preventive pharmacological treatment of migraine during pregnancy and lactation, and to give recommendations for clinical practice.

Treatment options during pregnancy**Acute treatment**

Medications for the treatment of acute migraine attacks include paracetamol, NSAIDs, triptans, opioid analgesics, ergot alkaloids, and antiemetics.

Paracetamol

Paracetamol (acetaminophen) has traditionally been considered a safe and well-established treatment option in all stages of pregnancy.¹⁹ Findings from three independent studies published in 2013–2014 have raised concern about adverse neurodevelopmental effects in children after long-term exposure (>28 days) to paracetamol *in utero*.^{20–22} The European Medicines Agency (EMA) has evaluated the findings from the first two studies, and concluded that current evidence is insufficient to support the association between paracetamol exposure in pregnancy and neurodevelopmental effects.²³ Thus, paracetamol remains the analgesic of choice during pregnancy, and although its efficacy in migraine is somewhat limited, it could be an option for treating mild to moderate attacks.²⁴

NSAIDs

NSAIDs are frequently used as antimigraine agents.^{24,25} Prostaglandins regulate several processes before, during and after pregnancy, including ovulation, decidualization, implantation, placentation, cervical ripening, uterine contractility and involution. In the fetus, prostaglandins mediate relaxation of smooth muscle cells in the *ductus arteriosus*, renal blood vessels and the systemic vasculature.^{26–29}

Adverse pregnancy outcomes following NSAID use differ according to trimester of exposure. NSAID use in early pregnancy has been associated with miscarriage^{30–32} and congenital malformations ([Supplementary Table 1](#)).^{33–35} The majority of studies evaluating the effect on miscarriage are large, prospective, and population-based. Nevertheless, the findings have often remained inconclusive owing to methodological issues associated with designating pregnancy outcomes, as well as confounding by indication, immortal time bias and a risk of exposure misclassification. The effect of these issues is further substantiated by the fact that some studies could not confirm an increased risk of miscarriage.^{36–39} Nevertheless, an increase in the risk of miscarriage after NSAID use in early pregnancy cannot be satisfactorily ruled out and also seems plausible from a pharmacological perspective.

Associations between prenatal NSAID exposure and congenital malformations have been assessed in studies covering more than 20,000 pregnancies ([Supplementary Table 1](#)).^{31,33–35,39–43} Some of the newer large and population-based prospective studies have found associations with congenital malformations.^{34,35} By contrast, other recent prospective population-based studies that were sufficiently large to rule out a twofold increase in risk, could not confirm these findings.^{40,42,44} In addition, one case–control study that specifically evaluated congenital heart defects did not find any association with maternal NSAID exposure.⁴³

Use of NSAIDs late pregnancy has been associated with premature closure of the *ductus arteriosus*,^{27,45,46} neonatal intraventricular haemorrhage,^{45,47,48} impaired renal function,^{45,49–51} persistent pulmonary hypertension of the newborn,^{52,53} necrotising enterocolitis,^{45,57} and cerebral palsy ([Supplementary Table 2](#)).⁵⁴ The plausibility of these reports from a pharmacological point of view warrants their findings to be taken into serious consideration. Three studies have analysed the effect of *in utero* NSAID exposure on birth weight and gestational age and found no significant relationship.^{31,39,40}

Finally, continuous preconceptional and periconceptional NSAID use might interfere with ovulation and implantation, thereby reducing the possibility of becoming pregnant.⁵⁵

In conclusion, owing to the suggested increase in the risk of miscarriage and congenital malformations, NSAIDs should preferably be avoided in the first trimester. In the second trimester and the early part of third trimester, the use of single doses of NSAIDs for treating acute migraine attacks is justified when both nonpharmacological therapy and paracetamol prove insufficient. Use of NSAIDs closer to term—we suggest after gestational week 32—should be avoided because of the increased risk of adverse fetal outcomes.

Triptans

Triptans act as serotonin 5-HT_{1B/1D/1F} receptor agonists.⁵⁶ 5-HT_{1B/1D} receptors are also found in the umbilical cord artery⁵⁷ and fetal brain.⁵⁸ Of the seven triptans available worldwide (sumatriptan, zolmitriptan, naratriptan,

rizatriptan, almotriptan, eletriptan and frovatriptan), the longest clinical experience of use during pregnancy exists for sumatriptan.

An overview of observational studies on the safety of triptan use during pregnancy is given in [Supplementary Table 3](#). A total of 10 studies, including more than 6,000 exposed infants, have evaluated pregnancy outcomes after maternal triptan use.^{59–68} Five of the studies included multiple triptans, whereas four studies evaluated sumatriptan only,^{65–68} and one rizatriptan only.⁶² The most frequently studied adverse pregnancy outcomes were spontaneous abortion, congenital malformations, prematurity or low gestational age, and low birth weight.

Risks of congenital malformations were evaluated in all studies; in the majority of studies, no such association was established. A large Swedish registry linkage study found an increased risk of congenital malformations following eletriptan use during the first trimester.⁶³ However, this association was based on three cases among 14 exposed infants, and there was no specific pattern to the malformations. The authors thus considered this finding as random. Two additional studies,^{60,64} including a higher number of women ($n = 189$ and $n = 179$, respectively), have evaluated the safety of eletriptan in early pregnancy; these data indicated no associations with congenital malformations. Spontaneous abortion was included as an outcome in six of the 10 studies, and one of these studies found an association with triptan use.⁶¹ Unfortunately, this study did not report the timing of exposure or specify which triptan was used. An association with atonic uterus has also been reported ([Supplementary Table 3](#)).⁶⁹

In general, most of the cited studies on triptans have methodological limitations. One of the major shortcomings is the lack of a disease comparison group, with an inability to rule out the impact of the underlying disease. Two studies, however, included a migraine control group made up of women not using triptans,^{66,68} and three studies included a migraine control group consisting of women who had used triptans before pregnancy only.^{60,64,67} In these studies, no increased risk of any adverse pregnancy outcomes was found in the triptan group compared with the migraine control group.

In conclusion, the findings from published studies on triptans are reassuring. Accumulated data suggest that sporadic use of sumatriptan is probably safe during pregnancy. However, despite the increased size of newer epidemiological studies, some still do not have sufficient power to detect rare adverse outcomes. Moreover, concern has been raised regarding the possibility that the vasoconstrictive effects of triptans could cause malformations related to vascular disruption, though no such evidence has been found in clinical studies. For triptans other than sumatriptan, safety documentation remains limited. We therefore suggest that sumatriptan should be the first choice if treatment with triptans is considered necessary during pregnancy. The guideline by the European Federation of Neurological Societies states that use of triptans in the first trimester is recommended if the fetus is more at risk from severe maternal

attacks with vomiting than from the potential adverse effects of triptan exposure.²⁵ However, such advice is of limited clinical utility, as the possible risks related to the two options cannot readily be quantified.

Opioid analgesics

Opioids have limited efficacy as antimigraine medications,²⁵ and their use should in general be discouraged owing to the risk of abuse and dependence.²⁴ A few studies have evaluated risks of congenital malformations after opioid exposure during the first trimester of pregnancy. A large case-control study indicated an increased risk of atrioventricular septal defects (adjusted OR [aOR] 2.0, 95% CI 1.2–3.6), hypoplastic left heart syndrome (aOR 2.4, 95% CI 1.4–4.1), spina bifida (aOR 2.0, 95% CI 1.3–3.2) and gastroschisis (aOR 1.8, 95% CI 1.1–2.9) after exposure in early pregnancy.⁷⁰ However, the study was limited by the potential of recall bias arising from retrospective reporting of drug intake during pregnancy. In addition, the increased relative risk of these defects corresponds to only a modest increase in absolute risk, given the low baseline rates.

A large population-based cohort study found that use of codeine during the third trimester was associated with acute caesarean delivery (aOR 1.6, 95% CI 1.2–2.2) and postpartum haemorrhage (aOR 1.4, 95% CI 1.1–1.7).⁷¹ No significant associations with other adverse pregnancy outcomes were found. Maternal use of opioids close to delivery can cause neonatal respiratory depression. Long-term use during pregnancy can also cause withdrawal symptoms in the newborn infant.¹⁹ Prolonged use should clearly be avoided during pregnancy, but for short-term and sporadic use, weak opioids such as codeine might be a rescue alternative when other agents have failed.

Ergot alkaloids

The evidence for efficacy of ergotamine and other ergot derivatives in acute migraine treatment is limited,²⁵ and these agents are, in any case, contraindicated during pregnancy because of their vasoconstrictive and uterotonic effects.⁷² One study found a notable increase in the proportion of low-birth-weight newborns (16.4% versus 5.7%; adjusted prevalence OR 2.8, 95% CI 1.2–6.5) and preterm births (16.4 versus 9.2%; adjusted prevalence OR 1.9, 95% CI 1.0–4.0) after maternal ergotamine use during pregnancy, probably related to ergotamine-induced placental vasoconstriction.⁷³

Antiemetics

Antiemetics are used as adjunctive medications to relieve migraine-associated nausea and vomiting, with the dopamine antagonists metoclopramide and domperidone as the recommended agents.²⁵ Metoclopramide has been reported to enhance the efficacy of orally administered sumatriptan,⁷⁴ possibly by promoting absorption, which can be impaired during a migraine attack due to gastric stasis.⁷⁵ In pregnancy, metoclopramide is commonly used in the treatment of hyperemesis gravidarum, and no association with congenital malformations or other harmful

fetal effects has been established.⁷⁶ Whereas the Canadian Headache Society recommends metoclopramide as the antiemetic of choice during pregnancy,²⁴ other guidelines state the contrary, arguing that metoclopramide should be avoided because of the risk of dyskinesia.²⁵ We have, however, not found any such reactions reported in the literature. Moreover, we consider this risk to be negligible, as extrapyramidal effects in infants after maternal intake of other dopamine antagonists (used as antipsychotic drugs) have only been reported with chronic use.

Safety data for domperidone in pregnancy is lacking. However, electrocardiographic QT-prolongation in newborns and infants has been reported following paediatric use of domperidone.⁷⁷ We therefore recommend that this drug should be avoided in pregnant women.

Preventive treatment

Medications commonly used for migraine prophylaxis include β -blockers, antiepileptic drugs, tricyclic antidepressants, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers and botulinum toxin type A (BTX-A). Of the various vitamin and mineral supplements available, the best-documented effects (classified as 'probably effective' by the American Academy of Neurology and the American Headache Society⁷⁸) exist for magnesium and riboflavin (vitamin B₂).

Preventive treatment is often recommended to be discontinued before pregnancy or when pregnancy is established, because migraine is ameliorated by pregnancy for most women. During pregnancy, prophylaxis has been advised in pregnant women with frequent (>3–4 per month) and prolonged severe attacks, especially for those women who do not respond to symptomatic treatment, or experience complications such as dehydration, anorexia and fetal stress.⁷²

Most of the safety documentation of preventive drugs stems from studies on pregnant women with other diseases, such as hypertension, epilepsy and depression. It should be borne in mind that use of these drugs in migraine could require different dosages than those used in conditions for which fetal effects have been studied, and that the fetal risks related to the underlying maternal disorder could differ as well.

β -blockers

β -blockers are shown to be effective in migraine prophylaxis, with the best evidence obtained for propranolol and metoprolol.^{25,79} A recent meta-analysis of 12 studies found no increased risk of all or major congenital malformations after first trimester exposure of β -blockers (OR 1.0, 95% CI 0.9–1.1), although an increased risk of cardiovascular (OR 2.0, 95% CI 1.2–3.4), orofacial (OR 3.1, 95% CI 1.8–5.4) and neural tube defects (OR 3.6, 95% CI 1.2–10.7) was reported.⁸⁰ The two latter associations, however, were mostly driven by oxprenolol, a nonselective lipophilic β -blocker, which is infrequently used today. The authors concluded that causality of these findings is difficult to interpret given the few and heterogeneous studies available. Moreover, recall bias

could be present in nine of the 12 studies. It should also be noted that there is an obvious risk of confounding by indication, as hypertension increases the risk of malformations.⁸¹

If preventive medications are considered necessary during pregnancy, metoprolol or propranolol in the lowest possible effective doses are suggested as first-choice options.⁸² The metabolism of metoprolol is markedly enhanced during pregnancy,⁸³ which could impair its clinical effect if the dose is not increased accordingly.

Use of β -blockers in the third trimester can induce fetal bradycardia, and newborns exposed to β -blockers close to delivery should be monitored for pharmacological effects such as bradycardia, hypotension and hypoglycaemia.⁸²

Antiepileptic drugs

Valproate and topiramate are the two antiepileptic drugs with the best evidence of efficacy in migraine prophylaxis.²⁵ Neither of these is considered safe during pregnancy. Valproate is clearly teratogenic, with an approximately 11% risk of malformations (mainly neural tube defects and cleft palate) after exposure *in utero*,⁸⁴ which is considerably higher than the 2–3% risk among children in the general population. Exposure in late pregnancy has been associated with adverse neurodevelopmental effects including autism, impaired cognitive function and reduced intelligence.^{84–86} Thus, valproate should be considered contraindicated as migraine prophylaxis in pregnant women.⁸⁷

Maternal use of topiramate in early pregnancy has been associated with an increased risk of oral clefts.^{88,89} Very limited data exist on late pregnancy exposure to topiramate, but low birth weight has been reported.⁹⁰ Moreover, unfavourable neurodevelopmental effects cannot be excluded considering the risk of such outcomes in most other antiepileptics. On the basis of these possible risks, topiramate should not be offered as preventive therapy for migraine in any stage of pregnancy.

Antidepressants

Of the tricyclic antidepressants used in the prevention of migraine, amitriptyline has the best-documented effect.²⁵ Use in pregnancy is controversial, despite little evidence of any major teratogenic potential. In one study, amitriptyline was found to increase the risk of pre-eclampsia in women with depression (RR 1.7, 95% CI 1.2–2.4).⁹¹ Data on exposure to antidepressants in late pregnancy is limited, but neonatal effects, including preterm birth, respiratory distress, and hypoglycaemia have been reported after maternal antidepressant use during the third trimester.⁹² Nevertheless, amitriptyline has been suggested as a second-line choice (after β -blockers) as preventive therapy in pregnant women.⁹³ Like for metoprolol,⁸³ it might be necessary to increase the dose of amitriptyline during pregnancy owing to its enhanced metabolism.

ACE inhibitors, ARBs and calcium channel blockers

Intrauterine exposure to ACE inhibitors and ARBs is associated with increased risk of adverse outcomes

in the fetus, including miscarriage, oligohydramnios, renal failure and death (intrauterine or after birth).^{94,95} Exposure to ACE inhibitors in early pregnancy has been associated with an increased risk of major congenital malformations (RR 2.7, 95% CI 1.7–4.3), including cardiovascular and CNS defects.⁹⁶ Hence, ACE inhibitors and ARBs are considered contraindicated at any stage in pregnancy.⁹⁴ The calcium channel blocker flunarizine should not be used during pregnancy owing to insufficient safety data.

Botulinum toxin type A

BTX-A is a purified neurotoxin isolated from the bacterium *Clostridium botulinum*. It is administered as intramuscular injections in the neck and head. Because of its high molecular weight, BTX-A is not expected to cross the placenta.⁹⁷ Only one case report for the treatment of migraine during pregnancy has been published.⁹⁸ Here, the patient received repeated injections from gestational week 18 with full resolution of migraine symptoms. The child was followed up for 6.5 years without detection of any neuromuscular or developmental adverse effects. Other reported cases are related to use of BTX-A during pregnancy for other indications, such as for cosmetic purposes. Reports of botulism during pregnancy also exist. These observations do not indicate that maternal treatment with BTX-A will adversely affect the fetus.⁹⁷ Nevertheless, owing to the very scarce data available, BTX-A should only be considered in exceptional treatment-refractory cases.

Magnesium and riboflavin

Magnesium has been widely used during pregnancy for other indications than migraine. Various magnesium salts are found in antacids as well as in laxatives. Magnesium sulphate is also used in the third trimester for the treatment of pre-eclampsia. There are no indications of any untoward maternal or fetal effects after such use, and in a recent study no neurological, cognitive or behavioural harms were detected in children followed up for 6–11 years after intrauterine exposure.⁹⁹ Magnesium use during pregnancy is, therefore, considered safe.

As there are no available data regarding fetal risks for riboflavin, this drug cannot be recommended during pregnancy in doses higher than those used for conventional vitamin supplementation.

Treatment options during breastfeeding

Human milk represents the ideal source of nutrients for small infants, and provides immunological and antioxidant protection superior to that of milk substitutes. As the infant should not unnecessarily be denied the benefits of breast milk, women are strongly encouraged to breastfeed whenever possible.¹⁰⁰ Thus, in addition to the possible risk related to drug exposure via breast milk, the disadvantage of not receiving breast milk should always be taken into account when performing a risk–benefit evaluation related to medications for lactating women.

In order to quantify infant drug exposure through milk for a fully breastfed infant, the relative infant dose (RID)

Box 1 | Breastfeeding and relative infant dose

Relative infant dose (RID)¹⁰¹ is the weight-adjusted dose of a drug received by the infant via breast milk, expressed as a percentage of the weight-adjusted maternal dose.

$$\text{RID} = \frac{\text{Infant daily dose (mg/kg)}}{\text{Maternal daily dose (mg/kg)}} \times 100$$

- RID <10%: breastfeeding is generally considered safe, with the exception of highly toxic agents
- RID ≥10%: it is generally assumed that a potential risk of pharmacological effects in the infant may exist

is one of the most central measures (Box 1). Another important factor is the infant age. As the processes for elimination of drugs gradually mature during the first months of life, even drugs with a relatively high RID, which preferably should be avoided in premature and newborn babies, can safely be given to a lactating mother whose infant is older.

Acute treatment

Paracetamol

Paracetamol is excreted in breast milk in low concentrations,¹⁰² and the metabolic capacity of paracetamol is about the same in neonates as in adults.¹⁰³ With the exception of one case report of a 2-month-old infant who developed a rash after exposure to paracetamol through breast milk,¹⁰⁴ no adverse effects in breastfed infants have been described in literature. On the basis of long clinical experience, paracetamol is considered safe during breastfeeding.^{24,103}

NSAIDs

In general, NSAIDs are considered compatible with breastfeeding, with ibuprofen being the drug of choice owing to its short elimination half-life (about 2 h), lack of active metabolites, and low excretion in milk.^{24,72} In addition, there are no adverse effects reported in breastfed infants.¹⁰³ In a recent review, diclofenac and naproxen were also regarded as compatible with breastfeeding, but caution is warranted because the risk profile is less certain.¹⁰⁵ We suggest that naproxen and diclofenac should be regarded as second choices within the NSAID group.

More controversies exist regarding the safety profile of aspirin. Thrombocytopenic purpura has been reported in an infant exposed to aspirin via breast milk.¹⁰⁶ As children exposed to salicylates have a theoretical risk of Reye syndrome, regular use during breastfeeding should be avoided.⁸² Occasional use of single doses, however, should not be expected to pose a risk to the infant.¹⁰³

Triptans

Making recommendations for triptan use is hindered by the lack of data. One study including five lactating women treated with a single, subcutaneous dose of sumatriptan found that the estimated RID was only 3.5%, suggesting that use of sumatriptan during lactation should not pose a substantial risk to the infant.¹⁰⁷ The Summary of Product Characteristics for sumatriptan

advises that breastfeeding should be avoided for 12 h after treatment.¹⁰⁸ We consider this precaution to be too conservative given the drug's short elimination half-life of about 2 h and its low oral bioavailability; we advise that the mother may breastfeed as soon as practically feasible after recovering from the migraine attack.

Eletriptan is suggested to be even safer than sumatriptan because its high plasma protein binding results in lower concentrations in breast milk than in case of sumatriptan.¹⁰⁹ Excretion of eletriptan in breast milk has been studied in eight women, and a maternal dose of up to 80 mg daily produced low levels in breast milk.¹⁰¹ The estimated RID of 0.2% would not be expected to cause any adverse effects in breastfed infants.

To date, there are no published data on other triptans. Until more safety data are provided, caution is recommended for the use of these triptans during lactation. As frovatriptan has a long half-life (25–30 h) compared with other triptans, we suggest that—until more data are available—this drug should be avoided in breastfeeding women, at least during the infant's first months of life.

Opioid analgesics

Administration of single doses of opioid analgesics is generally viewed as compatible with breastfeeding because, for most opioids, only low levels have been detected in milk.¹⁰³ Neonatal death has been reported in an infant whose mother used a paracetamol–codeine combination in therapeutic doses over a 13-day period following delivery.¹¹⁰ The infant gradually developed lethargy and had difficulties in feeding. The mother carried a *CYP2D6* allele associated with ultrarapid metabolism of codeine to morphine, which led the infant to be exposed to toxic levels of morphine in the breast milk. Thus, repeated dosing of codeine should be avoided. Some argue that maternal *CYP2D6* genotyping should be considered before prescribing codeine during breastfeeding,¹¹¹ but such a procedure does not seem justified if codeine is used occasionally in single doses. In general, sporadic use of opioids in the lowest effective analgesic dose could be a rescue alternative when other agents are ineffective.¹¹² However, particular caution should be taken when the infant is premature or newborn²⁴ owing to their impaired capacity to metabolize opioids.

Ergot alkaloids

As existing documentation is very scarce, use of ergotamine is not recommended in breastfeeding women. A study from 1934 reported vomiting, diarrhoea and convulsions in breastfed infants whose mothers used ergotamine for migraine, and on this basis different sources either strongly discourage prolonged use in nursing mothers¹⁰¹ or consider it contraindicated altogether.¹⁹ Moreover, ergotamine can inhibit prolactin secretion and thereby decrease milk production.¹⁰¹

Antiemetics

Metoclopramide is excreted in breast milk with RID values ranging from 4.7–14.3%,¹⁰¹ but infant plasma

concentrations after exposure via breast milk are low,¹¹³ and no adverse effects have been reported in breastfed infants. Thus, even though the RID is relatively high, metoclopramide in single doses would not be expected to cause any harmful effects in the infant, and could be considered compatible with breastfeeding.

Preventive treatment

β-blockers

β-blockers are suggested as first-choice medications if migraine prophylaxis is needed during lactation.⁹³ Propranolol is excreted into breast milk, but the infant doses are considerably lower than those used therapeutically in infants.¹¹⁴ Metoprolol is also excreted in breast milk to some extent, with an RID of 1.4%.¹⁰¹ As infant plasma concentrations are negligible, use during breastfeeding is not expected to pose a risk to the infant.^{115,116} Although symptoms caused by β-blockade (such as bradycardia and hypoglycaemia) have not previously been reported following exposure to propranolol or metoprolol via milk, some authors nevertheless recommend that exposed infants should be closely observed for these signs.¹¹⁷ Even though such effects perhaps could be an issue in preterm infants or newborns, we consider it unlikely that any such pharmacological effect would arise in a breastfed infant.

Antiepileptics

Valproate binds highly to plasma proteins, thereby limiting its passage into breast milk. The estimated RID is low, 1.4–1.7%.¹¹⁸ Moreover, infant plasma levels after exposure via breast milk are considerably lower than the therapeutic plasma concentrations in infants and children treated for seizures.¹¹⁸ Thus, valproate is considered compatible with breastfeeding. However, it has been argued that valproate is best avoided owing to its teratogenic potential should the lactating mother become pregnant again.⁹³

Data on the excretion of topiramate in human milk are limited. A study in five women found RID values of 3–23%.¹¹⁹ Infant drug levels were 10–20% of the maternal plasma levels, and in one infant the concentration was below the detectable level. No adverse effects were reported in the breastfed infants. Although topiramate is generally regarded as compatible with breastfeeding—despite a less documented safety profile than comparable drugs¹⁰⁵—it seems advisable to monitor at least the youngest infants for sedation, irritability, poor suckling, and diarrhoea, because of its relatively high RID values.

Antidepressants

Milk levels of amitriptyline and its active metabolite nortriptyline are low, with estimated RID values of 1.2–2.5%.¹²⁰ Adverse effects have not been reported in breastfed infants, and infant plasma levels have been reported to be very low. On the other hand, data are generally sparse, and other tricyclic antidepressants have elimination half-lives that are considerably longer in infants than in adults.¹²⁰ Therefore, accumulation

Table 1 | Safety of commonly used antimigraine medications over the course of pregnancy and during lactation

Medication	Close to conception	First trimester	Second trimester and early third trimester	Late third trimester	During lactation
Acute treatment*					
Paracetamol	Considered safe	Considered safe	Considered safe	Considered safe	Considered safe
Sumatriptan	No evidence of increased fetal or maternal risk	No evidence of increased risk of malformations	No evidence of increased fetal or maternal risk	No evidence of increased fetal or maternal risk	Considered safe
Other triptans	No evidence of increased fetal or maternal risk, but data are limited	No clear evidence of malformations, but data are limited	No evidence of increased fetal or maternal risk	No evidence of increased fetal or maternal risk	Most triptans are probably compatible with breastfeeding
NSAIDs: ibuprofen, diclofenac, naproxen	Possibly increased risk of miscarriage	Possibly increased risk of malformations	Single doses considered safe in second trimester; occasional use of single doses up to week 32 in the third trimester should not pose any risk to the fetus	Risk of harmful fetal and maternal effects if used after week 32	Generally compatible with breastfeeding, with ibuprofen being the drug of choice
Preventive treatment					
β-blockers: metoprolol, propranolol	No evidence of increased fetal or maternal risk	Occasional reports of increased risk of some malformations, but causality not established In general, no notable teratogenic effects demonstrated	Risk of adverse effects in the fetus, for example bradycardia	Risk of adverse effects in the newborn infant, for example bradycardia, hypotension and hypoglycaemia	Adverse effects in the infant are unlikely
Tricyclic antidepressants: amitriptyline	No evidence of increased fetal or maternal risk	Few data exist; no evidence for teratogenic effects for tricyclic antidepressants in general	Very few data exist; increased risk of pre-eclampsia in one study	Adverse effects and withdrawal symptoms in the newborn infant cannot be excluded	Low excretion in milk, but few data available Impaired elimination in premature and newborn infants might cause accumulation
Antiepileptics: valproate	Increased risk of neural tube defects in the fetus	Increased risk of a variety of malformations	Risk of unfavourable long-term neurodevelopmental effects	Risk of unfavourable long-term neurodevelopmental effects	No risk for the breastfed infant, but an obvious risk of teratogenic effects if the mother should become pregnant again
Antiepileptics: topiramate	No data exist, but experience with other antiepileptic drugs suggests it is wise to avoid use	Increased risk of orofacial clefts	Few data exist, but unfavourable mental and neuromotor effects in the child cannot be excluded	Few data exist, but unfavourable mental and neuromotor effects in the child cannot be excluded	Generally considered compatible with breastfeeding, but in premature and newborn infants, drug levels might accumulate to cause adverse effects

Overview of the safety of commonly used antimigraine medications related to stage of pregnancy and lactation. Dark green pills indicate drugs that are considered safe. Light green pills indicate drugs that are generally considered safe, but uncertainty exists owing to, for example, risks associated with specific drugs in a class or with a certain time period during pregnancy, or because of the limited data. Yellow pills indicate drugs for which increased risk of harm cannot be excluded, either because of studies revealing harmful effects or a lack of data supporting safety. Red pills indicate contraindicated drugs, for which the risk to the fetus or infant exceeds the therapeutic benefit to the mother. *Classification presupposes occasional use; risks may increase with frequent or excessive use.

cannot be excluded in premature and newborn babies. In such cases, caution could be warranted, and the infant should be monitored for signs such as sedation, poor suckling, and constipation. By contrast, in older infants, amitriptyline exposure through breast milk would not be expected to cause any adverse effects. Thus, amitriptyline could be considered as migraine prophylaxis in the postpartum period in cases where β-blockers are ineffective or contraindicated.⁹³

ACE inhibitors, ARBs and calcium channel blockers
Data on the excretion of ACE inhibitors and ARBs into milk are extremely scarce, with the exception of ACE inhibitor enalapril, for which RID values of 0.07–0.2% have been estimated. Even though such low concentrations would not be expected to pose any significant risk to the infant, enalapril is potentially nephrotoxic in premature or newborn infants and should be used with caution.¹⁰¹

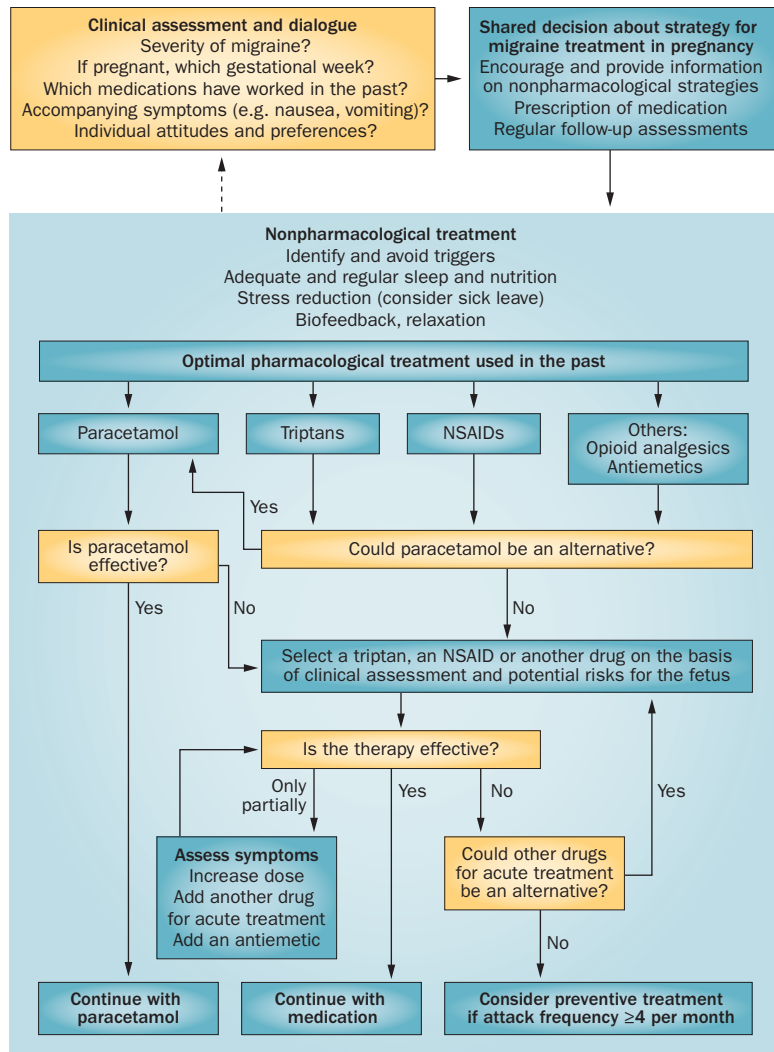


Figure 1 | Algorithm for the treatment of migraine in pregnant women. When medication is needed, paracetamol should be the first choice. If this drug is insufficiently effective within the recommended dosage range, limited use of triptans can be considered. Of these, sumatriptan is the first-choice, as its safety during pregnancy has been more extensively studied than for the other triptans. NSAIDs, preferably ibuprofen, can also be used under certain circumstances, although there are specific risks and contraindications related to intake in the first and third trimesters (Table 1). Opioids are generally not recommended, but from a teratogenic point of view, sporadic use should not pose any risk to the fetus. Thus, when used in single doses, short-acting opioids, such as codeine, can be an option when other antimigraine agents fail. Antiemetics, preferably metoclopramide, can be considered as conjunctive therapy in women experiencing disabling nausea and vomiting. According to current evidence of safety, the β -blockers propranolol and metoprolol are considered the drugs of choice when preventive treatment is needed.

No data exist on flunarizine excretion into milk, and no reports are found in literature regarding its use during lactation. Due to its very long elimination half-life in infants—19 days—use in breastfeeding women is discouraged.¹⁰⁵

Botulinum toxin type A

No reports on the use of BTX-A during lactation are described in literature. Because of its high molecular weight, the drug is not expected to appear in the systemic

circulation and would consequently not be excreted into breast milk.¹⁹

Magnesium and riboflavin

Magnesium is normally found in breast milk, and data from one study indicates that maternal intake of magnesium increases its concentration in milk only slightly.¹²¹ The RID of magnesium is estimated to be 0.2%. As the absorption of magnesium from the gut is poor, there is no reason to believe that surplus magnesium in breast milk would cause any substantial effects in the infant. Although even fewer data are available for riboflavin, this drug is also considered compatible with breastfeeding.¹⁰¹

Clinical recommendations

Before pregnancy

If relevant, all women of fertile age with migraine should be informed about any potential adverse effects that current medication might have on the fetus—even women who do not report contemplating pregnancy. Particular precautions should be taken with drugs with an established teratogenic risk. The EMA has recently stated that doctors should exclude pregnancy before prescribing valproate for women with migraine, and that it should not be prescribed to those who are not on effective contraception.⁸⁷ We recommend that topiramate, ACE inhibitors and ARBs should be stopped and avoided by women contemplating pregnancy, and women of fertile age using these drugs should be informed about adequate contraception. In general, discontinuation of preventive therapy is recommended before pregnancy or when pregnancy is established, because migraine is usually ameliorated by pregnancy itself.

In the periconceptional period, good counselling is particularly important, and should address the expected disease activity throughout pregnancy and the post-partum period, the potential teratogenic risks of still ongoing drug treatment (Table 1), and the alternative treatment options. To promote adherence to therapy, the dialogue should also focus on the woman's concerns, expectations, and knowledge about her medication.

During pregnancy

Nonpharmacological strategies should be the mainstay of treatment in pregnant women and always complementary when pharmacological treatment is required. Nevertheless, the possible risks associated with untreated or poorly managed migraine should be borne in mind, and absolute restrictions in pharmacotherapy are therefore not advisable. When medication is required, the aim is to provide the most effective treatment constituting the lowest possible risk to the fetus (Table 1). With many treatment options available, the medication regimen must be tailored to the individual patient, taking into consideration the frequency and severity of migraine attacks, accompanying symptoms, and the woman's previous drug experience and current preferences. Figure 1 presents a treatment algorithm in pregnant women. Regular follow-up assessments, preferably on a monthly basis, are recommended.

The postpartum period

Maternal wishes and expectations regarding breastfeeding and the choice of medication should be addressed well in advance of delivery. Women whose migraine improves during pregnancy should be informed about the likely return of symptoms following delivery.

None of the most commonly used drugs for acute treatment of migraine are transferred into breast milk in pharmacologically significant amounts. Thus, in most cases, breastfeeding could be encouraged, as the benefits of receiving breast milk by far outweigh any potential risks to the infant (Table 1). However, more research is needed to quantify infant exposure of the least studied agents, such as the newer triptans.

Conclusions

Several effective antimigraine medications are reasonably safe for use by pregnant and breastfeeding women. Nonpharmacological strategies are always first-line treatment options for mild migraine, and should also be used complementarily whenever pharmacological treatment is required. In pregnancy, prophylactic treatment should only be considered in the most severe cases. Women with

migraine should be offered periconceptional counselling to promote a safe, healthy pregnancy and postpartum period for mother and child.

Review criteria

A literature search was performed in Medline and Embase using the keywords “migraine”, “drug therapy”, “pregnancy”, “pregnancy outcome”, “birth defects”, “congenital malformations”, “breast milk”, “breastfeeding” and “lactation”, combined with the individual migraine medication or medication group considered. Medical Subject Headings (MeSH terms) were used when possible. For each relevant paper, the bibliography was scrutinized for additional citations. Only studies in humans, published in English were included. We consulted the migraine treatment guidelines from the American Academy of Neurology and the American Headache Society,^{78,79} the Canadian Headache Society,^{24,93} and the European Federation of Neurological Societies.²⁵ We also consulted textbooks and Internet resources on drug use during pregnancy and lactation (Supplementary further reading). Finally, the authors’ own clinical experience and research have been included in the material.

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Author contributions

O.S., S.A., H.N. and K.N.-H. wrote the article. All authors researched data for the article, provided substantial contribution to discussion of content and reviewed/edited manuscript before submission.

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In the section discussing treatment options during pregnancy, the last sentence under the subheading 'Antidepressants' should cite reference 83, not 84. The correction has been made to the print and online versions of the article.

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In the section discussing treatment options during pregnancy, subheadings 'Ergot alkaloids' and 'Antidepressants' should cite reference 25, not 23. In the section discussing treatment options during breastfeeding, subheadings 'Paracetamol' and 'Opioid analgesics' should cite reference 24, not 21; subheading 'Ergot alkaloids' should cite reference 19, not 24. The corrections have been made to the print and online versions of the article.