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Current concepts in migraine and their relevance to pregnancy

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Abstract

The prevalence of migraine in women of childbearing age is high, estimated at 24%. Migraine management during pregnancy and lactation can be challenging. Our understanding of the way in which medications affect the unborn fetus is still incomplete and the evidence is constantly changing with more recent emphasis on longitudinal studies and childhood development. The aim of this article is to describe the relationship between migraine and pregnancy and review the current evidence on treatment options in pregnancy and lactation.

Keywords

Migraine, pregnancy

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Migraine is estimated to affect 959m people worldwide. In women of childbearing age, the prevalence is highest at 24%.[1] It has a female preponderance of 3:1. This is thought to be due to the influence of female hormones as before puberty, both sexes are affected equally.

Pathophysiology of migraine

Functional imaging studies have provided evidence that there is disordered sensory processing in migraine with key involvement of deep brain structures; thalamus, hypothalamus and brainstem.[3,4] The current thinking is that there is activation of the trigeminovascular system with efferent fibres to the dura mater and cranial blood vessels, and the afferent projections from these structures to the trigeminocervical complex (TCC) at the cervicomedullary junction.[5]

Trigeminal sensory nerve fibres contain neuropeptides including calcitonin gene-related peptide (CGRP). This has also been found in the brainstem. In humans, CGRP has been shown to be elevated during the headache phase of migraine and levels normalise following triptans.[6]

Sensory afferents from the trigeminal system and cervical input synapse at the TCC via the trigeminal ganglion (TG) and cervical ganglion (CG). The ascending pathway is shown in blue and the descending modulatory pathway in red (see Figure 1). There is parasympathetic output via the sphenopalatine ganglion (SPG).

The effect of pregnancy on migraine

Migraine frequency and severity are thought to be affected by fluctuations of female hormones, in particular, oestrogen levels. This explains why there is often a menstrual trigger. Consequently, migraine has been reported in large studies to improve by the end of the third trimester in 67–89% of women[7,8] with a smaller prospective study documenting a 79% reduction.[9] This may also be due to an increase in endogenous endorphins. There may be an exacerbation of symptoms in the first trimester, partly due to lifestyle changes including missing meals due to nausea or vomiting of morning sickness. An improvement is often seen in the second trimester as oestrogen levels rise. Unfortunately, some women do not notice a benefit as the pregnancy progresses and others may see an exacerbation of their symptoms, often those with a history of migraine with aura.[7] These cases present a challenge to many physicians. The management of these will be discussed later. It is also well described for some women to present with migraine aura for the first time during pregnancy[10] and this is thought to be related to the increase in oestrogen levels. It is common for women to experience a post-partum exacerbation within 3–6 days as oestrogen levels fall and this is compounded by lifestyle changes such as sleep disturbance, irregular meal times, stress etc. There are some limited data suggesting that breast-feeding delays the recurrence of migraine back to pre-pregnancy levels[11] with a possible explanation that this may be related to anovulation.[9]

The effect of migraine on pregnancy

There have been a number of papers suggesting an association between migraine and preeclampsia or gestational hypertension.[12] More recently there has been some evidence suggesting an increase in pre-term births and low birth weight (OR 1.24 and 2.74, respectively).[13,14] However, there are possible confounding factors including medication taken during pregnancy which was not recorded in the study.

A population-based study in USA also found a link between migraine and vascular diseases such as stroke and myocardial

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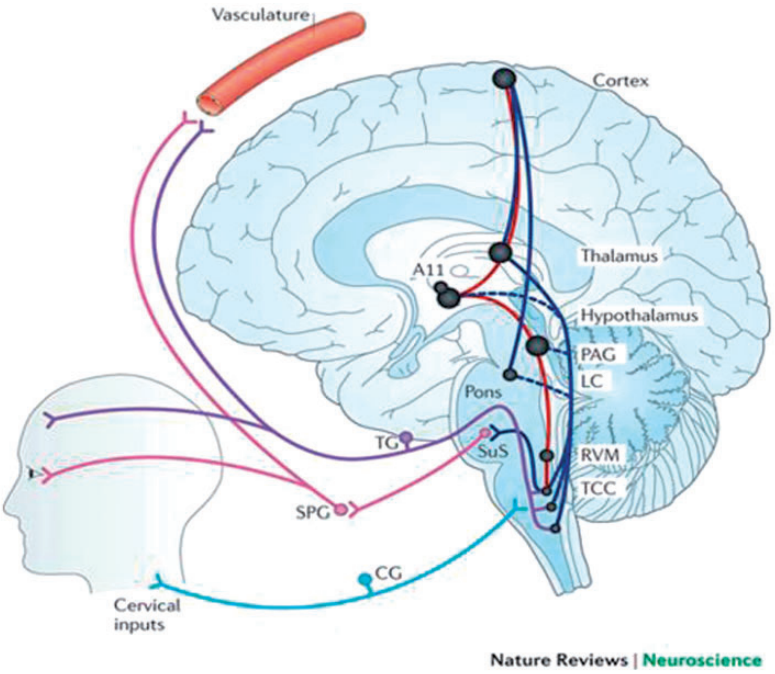

Figure 1. Neuronal pathways involved in migraine pathophysiology. Sensory afferents from the trigeminal system and cervical input synapse at the TCC via the trigeminal ganglion (TG) and cervical ganglion (CG). The ascending pathway is shown in blue and the descending modulatory pathway in red. There is parasympathetic output via the sphenopalatine ganglion (SPG).
TCC: trigeminocervical complex; PAG: periaqueductal grey; LC: locus coeruleus; RVM: rostoventral medulla.

infarction in pregnancy, although this relied on discharge coding and used International classification of diseases-9 (ICD-9) coding for migraine and excluded tension-type headache diagnosis on discharge. Since only 0.185% of their pregnant women were coded as having migraine it is likely that the coding is not sufficient to capture migraine.[15] A subsequent systematic literature review by Wabnitz and Bushnell et al. supported this association but included the above-referenced paper. Given the limitations described further studies are required to corroborate this link.[16]

Banhidy et al. reported an increased risk of limb deformities in migraineurs.[17] However, this study was limited by a number of factors; the diagnosis of migraine was based on retrospective questionnaires and perhaps due to this the prevalence of migraine was 2–3% in their study population with a similar number having 'other headache'. This is likely to be a significant underestimate. Also, maternal drug use was not adequately excluded as a confounder. More rigorous studies are needed to support this association.

Management during pregnancy

The management of women with migraine should include preconception counselling particularly if migraine preventatives are used as some, such as valproate and topiramate, may have to be stopped.

It is important to manage migraine optimally during pregnancy as there can be deleterious effects on the health of both mother and fetus as a result of prolonged vomiting or nutritional issues. Advice on avoiding triggers, for example, keeping a regular sleep pattern and not missing meals is important. There is also a role for behavioural interventions such as relaxation, biofeedback and stress management.[18]

The decision to use medications during pregnancy will involve a discussion about the risk benefit ratio and patients must be provided with information allowing them to make an informed choice. It is important to aim for the lowest effective dose and frequency. As pregnant women are excluded from drug trials, there is a reliance upon observational and retrospective data with regards to teratogenicity. The current evidence regarding migraine medications will be discussed.

Acute treatments

Paracetamol

Paracetamol has long been considered safe in pregnancy. There have some recent suggestions of hyperactivity and behavioural disorders linked to long-term paracetamol use during pregnancy.[19] However, the American Food and Drug Administration (FDA) has reviewed these and concluded that current evidence is insufficient to support this.[20]

Non-steroidal anti-inflammatories

Non-steroidal anti-inflammatories (NSAIDS) are often the first line of treatment in migraine. There have been concerns raised about possible increased risks of miscarriage,[21] although a large, historical cohort study did not support this association[22] with the exception of indomethacin. After 32 weeks, NSAIDs have been linked with

Table 1. International Headache Society criteria for migraine.[2]

Migraine without aura
- A. At least five attacks fulfilling criteria B–D
- B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
- C. Headache has at least two of the following four characteristics:
  1. Unilateral location
  2. Pulsating quality
  3. Moderate or severe pain intensity
  4. Aggravation by or causing avoidance of routine physical activity
- D. During headache at least one of the following:
  1. Nausea and/or vomiting
  2. Photophobia and phonophobia

Migraine with aura
- A. At least two attacks fulfilling criteria B and C
- B. One or more of the following fully reversible aura

Symptoms:
1. Visual
2. Sensory
3. Speech and/or language
4. Motor
5. Brainstem
6. Retinal

- C. At least two of the following four characteristics:
  1. At least one aura symptom spreads gradually over $\geq$5 min, and/or two or more symptoms occur in succession
  2. Each individual aura symptom lasts 5–60 min
  3. At least one aura symptom is unilateral
  4. The aura is accompanied, or followed within 60 min, by headache

premature closure of the ductus arteriosus and pulmonary hypertension. A prospective cohort study looked at four NSAIDs, ibuprofen, diclofenac, naproxen and piroxicam, in 6511 pregnant women.[23] Ibuprofen and diclofenac in the second trimester were associated with low birth weight (OR 1.7 and 3.1, respectively), although this may be confounded by the underlying inflammatory disorders for which the patients were being treated. Second and third trimester use of ibuprofen was associated with an OR of 1.5 of asthma in 18-month olds. Third trimester diclofenac was also associated with maternal vaginal bleeding. Reassuringly, the study found no association with congenital malformations. It is reasonable to use ibuprofen or naproxen in the second and early third trimesters and there is no clear consensus on first trimester use.

Aspirin appears to be safe at low dose (<100 mg). Higher doses should be avoided in the third trimester due to risk of postpartum and neonatal bleeding as well as premature ductus arteriosus closure.

Naproxen 500 mg with a prokinetic anti-emetic such as metoclopramide can be an effective combination to give acutely.

Triptans

The triptans are 5-HT 1B/D agonists which are specific abortive agents in migraine (and cluster headache). Sumatriptan was the first and most commonly used although there are now several different triptans on the market.

There have been relatively large numbers of pregnant women exposed to triptans with data from pregnancy registries in Scandinavia contributing for the most part. The Norwegian Mother and Child Cohort Study was an observational, prospective study collecting data on 69,929 pregnant women, 1535 of whom were using triptans.[24] Sumatriptan was used by 47% of the triptan users in the first trimester; rizatriptan by 23.6%, zolmitriptan by 17.5% and eletriptan by 12.9%. No significant associations between triptan therapy during the first trimester and major congenital malformations were found but a slight increase in the risk of atonic uterus and haemorrhage was associated with triptan use during the second and/or third trimesters. A larger Swedish study used the national pregnancy register and medical birth register, and looked at 2777 pregnant women exposed to triptans, the majority on sumatriptan.[25] It again showed no evidence of teratogenicity. Unlike the Norwegian study, there was no increased risk for bleeding around delivery. A meta-analysis of 4208 exposed infants confirms the lack of evidence for teratogenicity but included two small studies ($n = 96$, $n = 82$) which suggested an increased risk of spontaneous abortion.[26] This increased risk was not found to be significant in the triptan-exposed group versus the migraine no-triptans group but was significant when comparing triptan-exposed to non-migraineurs. A subsequent prospective study of 432 women exposed to triptans does not corroborate this association.[27]

Table 2. Top choice acute migraine treatments during pregnancy and lactation.

Drug	First trimester	Second trimester	Third trimester	Lactation
Paracetamol	√	√	√	√
Ibuprofen/naproxen	(√)	√	√[a]	√
Sumatriptan	√	√	√	√
Metoclopramide	√	√	√	√

[a]Before 32 weeks.

A proportion of those from the Norwegian cohort completed validated questionnaires about their child at 18 months and 36 months and on the basis of these, it has been suggested that prenatal triptan use may be associated with externalizing behaviour problems (1.36-fold risk).[28] There are a number of possible confounders including severity of migraine and these findings should be interpreted with caution. Further studies are needed in this area.

If simple analgesics have failed, it is reasonable to prescribe sumatriptan following an informative consultation with the patient.

Ergotamines are used less often these days and are avoided during pregnancy due to potential vasoconstrictive and uterotonic effects. A recent observational study did not find any increase in congenital malformations but there was an increase in pre-term births.[25]

Opioids

The use of opioids in migraine, in general, is discouraged due to risk of dependence and the availability of better drugs.[29] Prolonged use in pregnancy is associated with neonatal withdrawal, growth retardation and respiratory depression late in pregnancy. Occasional use of weaker opioids such as codeine is reasonable if other drugs have failed.

Antiemetics

The dopamine antagonists, metoclopramide and domperidone are useful in migraine due to their prokinetic effect aiding absorption of oral medications as well their anti-emetic effect. Metoclopramide is often used in pregnancy for hyperemesis and is generally thought to be safe,[30] although there is a risk of dyskinesia. Domperidone is less likely to cause central effects such as dystonic reactions or sedation as it doesn't readily cross the blood-brain barrier but it has been rarely linked to prolonged QT on electrocardiogram and there are less data on safety in pregnancy.[31] Prochloperazine may be associated with neonatal withdrawal during third trimester use, although it is commonly used in clinical practice.[32]

Greater occipital nerve blocks

This is a peripheral block to the greater occipital nerve (GON) and is administered in headache centres for the temporary relief of primary headache disorders such as migraine.[33] It can be used to manage an acute, prolonged migraine episode as well as for chronic migraine. Cervical afferents from the GON synapse on second-order neurons in the TCC (see Figure 1). The lidocaine component of the GON is relatively safe. A steroid component, such as depomedrone, is often added to this peripheral block. A retrospective study of pregnant women receiving lidocaine or bupivicaine nerve blocks suggested that this could be an effective and safe treatment, although the study included only 13 patients.[34]

Preventative treatment

Women with more frequent or severe migraine may require treatment with migraine preventatives but these are generally initiated under the guidance of a neurologist and so will not be covered in detail. Ideally preventatives should be avoided, but if required beta-blockers, such as propranolol, are the first-line option and can be continued during breastfeeding. There are theoretical concerns about the use of beta-blockers in the third trimester and the development of neonatal bradycardia, hypoglycaemia or respiratory depression in the neonate. However, these are used in many women for a variety of indications and the majority do not experience any neonatal complications. Amitriptyline or nortriptyline are the second-line options with potential neonatal withdrawal symptoms when used late in the third trimester.[35] Topiramate, valproate and candesartan are contraindicated. A case report of Onabotulinumtoxin A injections for migraine from week 18 was published with no apparent adverse effects.[36] It is not generally used in clinical practice during pregnancy due to potential toxicity, although there is no clear evidence of teratogenicity. Although there is no evidence that melatonin is harmful in pregnancy, it is not recommended due to the lack of safety data. Acupuncture is thought to be safe.

Dietary supplements

Certain dietary supplements may have a beneficial effect in migraine although in comparison to pharmacological treatments, the evidence is less robust. Data in pregnancy are even more sparse than with pharmaceutical drugs, however.

Magnesium has long been used in pregnancy for other indications and considered safe, although recently intravenous magnesium sulphate exposure has been shown to be associated with fetal bone abnormalities.[37] It is not clear whether these effects occur following long-term oral magnesium supplementation at doses required for migraine prophylaxis.

Although riboflavin is safe in pregnancy at the recommended daily dose, there are no safety data in pregnancy on high doses (400 mg) required for migraine prophylaxis. Coenzyme Q may be a potential option as it has been used in preeclampsia from week 20 but other than this there is very little safety data.[38] Feverfew and butterbur are not recommended in pregnancy.

Breast feeding

Since over half of women experience a recurrence of migraine within the first post-partum month, breastfeeding mothers are likely to require some medication. As with pregnancy, recommendations on the use of drugs in lactation also largely rely on case reports and observational data. There are directories available such as the Hale manual.[39] The degree of safety of drugs is linked to the transfer into breast milk with an infant dose of less than 10% of the maternal considered to be relatively safe. Methods to reduce infant exposure include expressing milk, alternating between breast and bottle feed and altering the timing of feed to avoid peak levels in breast milk. The ability of the infant to metabolise drugs also depends on age with those less than one-month old most at risk and a better metabolism of drugs above seven months of age.[40]

With regards to acute medications, paracetamol and ibuprofen are the safest (Table 2). Available data suggest some of the other NSAIDS such as diclofenac do not pose a significant risk. Aspirin, however, should only be used with caution due to an association with Reye's syndrome in infants. Among the triptans, eletriptan has been demonstrated to have minimal transfer with 0.02% of the dose present although this was at 24 h.[41] Oral sumatriptan has poor bioavailability and it thought to be safe with an estimated 0.03% of the maternal dose. Subcutaneous sumatriptan reaches peak dose at 2.5 h with 3.5% relative infant dose.[42] Expressing and discarding milk for 8 h post subcutaneous injection would avoid any exposure but it is likely to be unnecessary unless the infant is pre-term.

Ergotamines are generally avoided. Codeine has been associated with infant apnoea and sedation in higher doses.

Anti-emetics such as metoclopramide and domperidone may increase prolactin and lactation, although domperidone has lower concentrations in milk.[43] Domperidone has, in fact, been given to breastfeeding mothers to increase lactation and is thought to be safe at doses of 30 mg per day or less. European Medicines Agency guidance recommends that it should be used at the lowest effective dose for the shortest possible duration with a maximum treatment duration of no more than one week due to the risk of cardiac arrhythmia.[44]

Occasional use of prochlorperazine is thought to be compatible with breastfeeding, although there is a risk of sedation and apnoea in younger infants.[45]

Current evidence suggests that it is reasonable to use these drugs with the relevant cautions noted in the text.

Novel treatments

There are a number of non-invasive neurostimulation devices available for the treatment of migraine including transcranial magnetic stimulation (TMS), vagal nerve stimulators and transcutaneous supraorbital nerve stimulators. These devices are placed on the head or neck and emit electrical signals to the nerve or magnetic pulses, in the case of TMS, to the occipital cortex. The mechanism of action has not been clearly established but they have been used to abort an attack and also as prophylaxis. The safety of non-invasive stimulation devices has not been determined in pregnancy. Data are limited but there have been case reports of three pregnant women treated with TMS with no complications documented[46] and anecdotal use of the other devices. These devices may offer a suitable alternative to drugs in the future, although further data are needed to establish safety.

There are some exciting developments in the world of migraine. As mentioned earlier, CGRP is expressed peripherally and centrally in migraine. CGRP antagonists have been developed and are likely to be used acutely to abort attacks as an alternative to triptans since they lack the vasoconstrictor effect of triptans. CGRP monoclonal antibodies have been shown to be effective as prophylactics.[6,47,48] Other drugs, including 5HT-1F receptor agonists which also lack the vasoconstrictor effects of triptans, are likely to become available in the near future, making them suitable for use in patients with cardiovascular conditions.[49] The suitability of these new drugs for pregnant migraineurs is unlikely to be known until these drugs have become well-established.

Our understanding of the way in which medications affect the unborn fetus is still incomplete and the evidence is constantly

changing with more recent emphasis on longitudinal studies and childhood development. The therapeutic landscape of migraine continues to evolve bringing with it the potential for better treatments for pregnant women in the future.

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References

1. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007; 68: 343–349.
2. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33: 629–808.
3. Afridi SK, Giffin NJ, Kaube H, et al. A positron emission tomographic study in spontaneous migraine. *Arch Neurol* 2005; 62: 1270–1275.
4. May A. Understanding migraine as a cycling brain syndrome: reviewing the evidence from functional imaging. *Neurol Sci* 2017; 38: 125–130.
5. Akerman S, Holland PR and Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. *Nat Rev Neurosci* 2011; 12: 570–584.
6. Karsan N and Goadsby PJ. CGRP mechanism antagonists and migraine management. *Curr Neurol Neurosci Rep* 2015; 15: 25.
7. Granella F, Sances G, Zanferrari C, et al. Migraine without aura and reproductive life events: a clinical epidemiological study in 1300 women. *Headache* 1993; 33: 385–389.
8. Melhado EM, Maciel JA Jr and Guerreiro CA. Headache during gestation: evaluation of 1101 women. *Can J Neurol Sci* 2007; 34: 187–192.
9. Sances G, Granella F, Nappi RE, et al. Course of migraine during pregnancy and postpartum: a prospective study. *Cephalalgia* 2003; 23: 197–205.
10. MacGregor EA. Oestrogen and attacks of migraine with and without aura. *Lancet Neurol* 2004; 3: 354–361.
11. Marcus DA, Scharff L and Turk D. Longitudinal prospective study of headache during pregnancy and postpartum. *Headache* 1999; 39: 625–632.
12. Adeney KL, Williams MA, Miller RS, et al. Risk of preeclampsia in relation to maternal history of migraine headaches. *J Matern Fetal Neonatal Med* 2005; 18: 167–172.
13. Chen HM, Chen SF, Chen YH, et al. Increased risk of adverse pregnancy outcomes for women with migraines: a nationwide population-based study. *Cephalalgia* 2010; 30: 433–438.
14. Facchinetti F, Allais G, Nappi RE, et al. Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. *Cephalalgia* 2009; 29: 286–292.
15. Bushnell CD, Jamison M and James AH. Migraines during pregnancy linked to stroke and vascular diseases: US population based case-control study. *BMJ* 2009; 338: b664.
16. Wabnitz A and Bushnell C. Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature. *Cephalalgia* 2015; 35: 132–139.
17. Banhidy F, Acs N, Horvath-Puho E, et al. Maternal severe migraine and risk of congenital limb deficiencies. *Birth Defects Res Part A Clin Mol Teratol* 2006; 76: 592–601.
18. Penzien DB, Irby MB, Smitherman TA, et al. Well-established and empirically supported behavioral treatments for migraine. *Curr Pain Headache Rep* 2015; 19: 34.
19. Liew Z, Ritz B, Rebordosa C, et al. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatr* 2014; 168: 313–320.
20. FDA. FDA has reviewed possible risks of pain medicine use during pregnancy. Drug Safety Communications, 2015. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm429117.htm
21. Li DK, Liu L and Odouli R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ* 2003; 327: 368.
22. Daniel S, Koren G, Lunenfeld E, et al. Fetal exposure to non-steroidal anti-inflammatory drugs and spontaneous abortions. *CMAJ* 2014; 186: E177–E182.
23. Nezvalova-Henriksen K, Spigset O and Nordeng H. Effects of ibuprofen, diclofenac, naproxen, and piroxicam on the course of pregnancy and pregnancy outcome: a prospective cohort study. *BJOG* 2013; 120: 948–959.
24. Nezvalova-Henriksen K, Spigset O and Nordeng H. Triptan exposure during pregnancy and the risk of major congenital malformations and adverse pregnancy outcomes: results from the Norwegian Mother and Child Cohort Study. *Headache* 2010; 50: 563–575.
25. Kallen B, Nilsson E and Otterblad OP. Delivery outcome after maternal use of drugs for migraine: a register study in Sweden. *Drug Saf* 2011; 34: 691–703.
26. Marchenko A, Etwel F, Olutunfese O, et al. Pregnancy outcome following prenatal exposure to triptan medications: a meta-analysis. *Headache* 2015; 55: 490–501.
27. Spielmann K, Kayser A, Beck E, et al. Pregnancy outcome after anti-migraine triptan use: a prospective observational cohort study. *Cephalalgia* 2017: 333102417724152.
28. Wood ME, Lapane K, Frazier JA, et al. Prenatal triptan exposure and internalising and externalising behaviour problems in 3-year-old children: results from the Norwegian Mother and Child Cohort Study. *Paediatr Perinat Epidemiol* 2016; 30: 190–200.
29. Amundsen S, Nordeng H, Nezvalova-Henriksen K, et al. Pharmacological treatment of migraine during pregnancy and breastfeeding. *Nat Rev Neurol* 2015; 11: 209–219.
30. Pasternak B, Svanstrom H, Molgaard-Nielsen D, et al. Metoclopramide in pregnancy and risk of major congenital malformations and fetal death. *JAMA* 2013; 310: 1601–1611.
31. Choi JS, Han JY, Ahn HK, et al. Fetal and neonatal outcomes in women taking domperidone during pregnancy. *J Obstet Gynaecol* 2013; 33: 160–162.
32. Administration UFaD. FDA Drug Safety Communication: antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. 2011. Available at: https://www.fda.gov/drugs/drugsafety/ucm243903.htm#sa

33. Afridi SK, Shields KG, Bhola R, et al. Greater occipital nerve injection in primary headache syndromes–prolonged effects from a single injection. *Pain* 2006; 122: 126–129.
34. Govindappagari S, Grossman TB, Dayal AK, et al. Peripheral nerve blocks in the treatment of migraine in pregnancy. *Obstet Gynecol* 2014; 124: 1169–1174.
35. Kallen B. Neonate characteristics after maternal use of antidepressants in late pregnancy. *Arch Pediatr Adolesc Med* 2004; 158: 312–316.
36. Robinson AY and Grogan PM. OnabotulinumtoxinA successfully used as migraine prophylaxis during pregnancy: a case report. *Mil Med* 2014; 179: e703–e704.
37. Yokoyama K, Takahashi N, Yada Y, et al. Prolonged maternal magnesium administration and bone metabolism in neonates. *Early Hum Dev* 2010; 86: 187–191.
38. Teran E, Hernandez I, Nieto B, et al. Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. *Int J Gynaecol Obstet* 2009; 105: 43–45.
39. Hale T and Rowe HE. *Medications & mothers' milk*. 17th edn. Springer Publishing, 2017.
40. Wells RE, Turner DP, Lee M, et al. Managing migraine during pregnancy and lactation. *Curr Neurol Neurosci Rep* 2016; 16: 40.
41. Hutchinson S, Marmura MJ, Calhoun A, et al. Use of common migraine treatments in breast-feeding women: a summary of recommendations. *Headache* 2013; 53: 614–627.
42. Wojnar-Horton RE, Hackett LP, Yapp P, et al. Distribution and excretion of sumatriptan in human milk. *Br J Clin Pharmacol* 1996; 41: 217–221.
43. Asztalos EV, Campbell-Yeo M, da Silva OP, et al. Enhancing human milk production with domperidone in mothers of preterm infants. *J Hum Lact* 2017; 33: 181–187.
44. European Medicines Agency. Restrictions on the use of domperidone-containing medicines. 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Domperidone_31/European_Commission_final_decision/WC500172573.pdf
45. Kauppila A, Arvela P, Koivisto M, et al. Metoclopramide and breast feeding: transfer into milk and the newborn. *Eur J Clin Pharmacol* 1983; 25: 819–823.
46. Bhola R, Kinsella E, Giffin N, et al. Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: evaluation of outcome data for the UK post market pilot program. *J Headache Pain* 2015; 16: 535.
47. Goadsby PJ, Reuter U, Hallstrom Y, et al. A Controlled trial of erenumab for episodic migraine. *N Engl J Med* 2017; 377: 2123–2132.
48. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the Preventive treatment of chronic migraine. *N Engl J Med* 2017; 377: 2113–2122.
49. Raffaelli B, Israel H, Neeb L, et al. The safety and efficacy of the 5-HT 1F receptor agonist lasmiditan in the acute treatment of migraine. *Expert Opin Pharmacother* 2017; 18: 1409–1415.