UNIVERSITEIT GENT

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

Academiejaar 2018 – 2019

Sex hormones and pregnancy in headache disorders.

Zoë DELARUELLE

Promotor: Prof. Dr. K. Paemeleire

Masterproef voorgedragen in de master in de specialistische geneeskunde
Neurologie

UNIVERSITEIT GENT

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

Academiejaar 2018 – 2019

Sex hormones and pregnancy in headache disorders.

Zoë DELARUELLE

Promotor: Prof. Dr. K. Paemeleire

Masterproef voorgedragen in de master in de specialistische geneeskunde
Neurologie

Voorwoord

Hoofdpijn is de meest frequente klacht voor ambulante doorverwijzing naar een neuroloog. Deze subdiscipline blijft dan ook een zwaargewicht binnen de neurologie. Uit de analyse van de Global Burden of Disease Study van 2017 blijkt dat migraine zowel voor de wereldwijde prevalentie, ongeacht leeftijd of geslacht, maar ook voor het aantal jaren 'lived with disability' reeds jaren in de top 3 staat.

Hoofdpijn komt voor bij beide geslachten, maar de 3 meest frequente primaire hoofdpijnsyndromen, spanningstype hoofdpijn, migraine en clusterhoofdpijn, blijken een verschillende prevalentie bij man en vrouw te hebben. Ook de zwangerschap en andere hormonale veranderingen in het leven lijken een impact te hebben op de prevalentie en het verloop van verschillende hoofdpijnsyndromen. In deze masterproef worden 2 artikels gebundeld die zich hierop toespitsen. Beide publicaties zijn het resultaat van een internationale samenwerking in kader van de School of Advanced Studies uitgaande van de European Headache Federation.

Negro et al. The Journal of Headache and Pain (2017) 18:106
DOI 10.1186/s10194-017-0816-0

The Journal of Headache and Pain

REVIEW ARTICLE Open Access

Headache and pregnancy: a systematic review

A. Negro[1*], Z. Delaruelle[2], T. A. Ivanova[3], S. Khan[4], R. Ornello[5], B. Raffaelli[6], A. Terrin[7], U. Reuter[6], D. D. Mitsikostas[8*] on behalf of the European Headache Federation School of Advanced Studies (EHF-SAS)

Abstract

This systematic review summarizes the existing data on headache and pregnancy with a scope on clinical headache phenotypes, treatment of headaches in pregnancy and effects of headache medications on the child during pregnancy and breastfeeding, headache related complications, and diagnostics of headache in pregnancy. Headache during pregnancy can be both primary and secondary, and in the last case can be a symptom of a life-threatening condition. The most common secondary headaches are stroke, cerebral venous thrombosis, subarachnoid hemorrhage, pituitary tumor, choriocarcinoma, eclampsia, preeclampsia, idiopathic intracranial hypertension, and reversible cerebral vasoconstriction syndrome. Migraine is a risk factor for pregnancy complications, particularly vascular events. Data regarding other primary headache conditions are still scarce. Early diagnostics of the disease manifested by headache is important for mother and fetus life. It is especially important to identify "red flag symptoms" suggesting that headache is a symptom of a serious disease. In order to exclude a secondary headache additional studies can be necessary: electroencephalography, ultrasound of the vessels of the head and neck, brain MRI and MR angiography with contrast ophthalmoscopy and lumbar puncture. During pregnancy and breastfeeding the preferred therapeutic strategy for the treatment of primary headaches should always be a non-pharmacological one. Treatment should not be postponed as an undermanaged headache can lead to stress, sleep deprivation, depression and poor nutritional intake that in turn can have negative consequences for both mother and baby. Therefore, if non-pharmacological interventions seem inadequate, a well-considered choice should be made concerning the use of medication, taking into account all the benefits and possible risks.

Keywords: Pregnancy, Breastfeeding, Headache, Migraine, Complications, Treatment, Adverse events

Introduction

Headache is the most frequent referral for neurologic consultation in the outpatient setting. The last release of data at 2013 from the Global Burden of Disease (GBD) - described now as "the most comprehensive worldwide observational epidemiological study to date" [1] - established headache disorders collectively as the seventh highest cause of years lived with disability (ylds) [2].

In front of a patient complaining about headache, the first purpose is to distinguish a primary headache (when pain *is the disease*) from a secondary headache (when pain *is a symptom of another disease*). More strictly, this is the main concern with a pregnant woman suffering from this symptom. Three scenarios are possible [3, 4]:

1. She suffers from a primary headache and now she presents with her usual headache;
2. She does not suffer from a primary headache and she presents with her first severe headache during pregnancy;
3. She suffers from a primary headache, but now pain is different in quality, intensity or associated symptoms.

In the second and third scenarios, headache must be considered as a symptom of an underlying disease until an appropriate diagnostic evaluation has been performed.

This systematic review is a summary of existing data on headache and pregnancy with a focus on clinical headache phenotypes, treatment of headaches in pregnancy

* Correspondence: andrea.negro@uniroma1.it
[1]Department of Clinical and Molecular Medicine, Regional Referral Headache Centre, Sapienza University of Rome, Sant'Andrea Hospital, 00189 Rome, Italy
[8]Neurology Department, Aeginition Hospital, National and Kapodistrian University of Athens, 11528 Athens, Greece
Full list of author information is available at the end of the article

and effects of headache medication on the child during pregnancy and breastfeeding, headache-related complications, and diagnostics of headache in pregnancy.

Methods of review

Two independent reviewers conducted an independent search on pubmed using the search terms "pregnancy" and "headache" OR "migraine", each combined with "complications" OR "treatment" OR "management". This search was carried out on June 15th, 2017. We included articles from the past 20 years. The initial screening was conducted based on eligibility of titles and abstracts. Original works, randomized, placebo- or comparator-controlled trials, published in full, were primarily selected for the review. Other references quoted include: systematic reviews, open label studies, retrospective studies, population-based studies, guidelines, manufacturers product monographs and letters to the editor. Discrepancies between reviewers were resolved by discussion.

Clinical headache phenotypes and observational studies in pregnancy

Primary headaches

In most cases headache is a primary disorder, including migraine and tension-type headache (TTH) as the more frequent conditions that affect women asking medical consultation. Several observational studies have been conducted to evaluate the course of primary headaches during pregnancy (Table 1). During pregnancy, primary headaches also showed a tendency to change in pattern from migraine without aura (MO) to migraine with aura (MA) and vice versa or from MO to TTH and vice versa: in an Italian study 9% of TTH patients developed MO during gestation, while 10% did the opposite [5]. Up-to-date, TTH is not correlated with any adverse pregnancy outcomes, even if sample size of the available studies are too small to achieve definitive conclusions [4].

Migraine

On the wake of the first pioneering articles [6, 7], following retrospective and prospective studies dealing with migraine and pregnancy published in the last twenty years show similar results. About one half to three fourths of female migraineurs experience a marked improvement in migraine during pregnancy with a significant reduction in frequency and intensity of their attacks, if not a complete resolution (Table 1) [8–18]. The remaining attacks show a progressive reduction in the mean pain intensity and duration as pregnancy proceeds [13, 17]. As a consequence, the 1-year headache prevalence of migraine and non-migrainous headache is lower among nulliparous pregnant women than in non-pregnant women [19]. Maggioni et al. Reported an absolute improvement during the first trimester, with a further reduction during the second and third ones [5], a data that has been confirmed by more recent studies [9, 13]. Differently, the Head-HUNT study found a marked reduction in headache burden only in the third trimester [19]. About 50% of the pluripara mothers present a persistent worsening of their headache with following gestations [5]. This is in line with the evidence that multiparous subjects more likely experience worsening of headache [9]. Other studies showed no significant differences between primi- and multiparous pregnant women as regards the course of headaches during gestation among migraineurs [17, 19], neither confirming the trend of further improvement after the first trimester [10]. A large Italian study found that the percentage of remissions during pregnancy was significantly higher in the subgroup of patients whose migraine started at menarche and in those suffering from menstrual migraine [8], even if this last data has not been confirmed by following studies [10, 13, 14].

Migraine without aura (MO) can start during pregnancy in 1 up to 10% of pregnant women [5, 15–17, 20], with some retrospective data rising up to 16.7% [13]; this is classically considered a first trimester phenomenon [5–7, 20]. In other cases, migraine can worsen during pregnancy, especially in the first trimester: this is reported in 8% of cases (Table 1) [5, 8–16]. Except for a few works concerning headache frequency [5, 13, 15], most articles analyse headache modifications during pregnancy without distinguishing between frequency and intensity of the attacks. A mean of 25% of MO patients will continue to have attacks during pregnancy, with hyperemesis, pathological pregnancy course and pre-gestation menstrual-related migraine being linked with this lack of improvement [13, 21]. Up-to-date, scientific literature lacks of large and rigorous studies aimed at understanding factors possibly associated with the absence of a clinical improvement during pregnancy [22, 23].

The relationship between estrogens fluctuations and MA has been the focus of fewer studies. MA starts or worsens during pregnancy more frequently than MO does: onset during gestation is reported in 10.7 up to 14% of cases [5, 11], worsening covers 8.4% of MA women (Table 1), with "no change" in pain pattern representing the most frequent evolution during gestation. Nearly half patients with MA will continue to have attacks [11]. This trend to recede in a lower number of cases than MO has been transversely confirmed [5, 13, 14], with rare exceptions [16]. It could be due to increased endothelial reactivity in MA patients compared with MO ones [21]. MA can develop new aura symptoms during gestation [24, 25], as pregnancy may trigger attacks of aura without headache as well [26]. In less frequent cases, hemiplegic migraine makes the differential diagnosis very difficult, especially in the third trimester [27, 28]. Therefore, we can easily understand why transient neurologic symptoms during

Table 1 Primary headaches course during pregnancy

Author	Study design	Sample size	Improvement or remission (%)	Unchanged (%)	Worsening (%)	Extra data
Migraine without aura						
Granella et al. [8]	R	571	67.3	29.2	3.5	Full sample size: 1300 women; 943 had had pregnancies; 571 women with migraine before first pregnancy
Scharff et al. [9]	P	19	56.7	36.6	6.7	Full sample size: 30; 11/30 with headache onset during pregnancy
Maggioni et al. [5]	R	81	89.5	7.7	2.5	Full sample size: 430 women, interviewed 3 days after delivery; among them, 81 MO, 12 MA, 33 TTH
Marcus et al. [10]	P	49	40.8	51	8.2	16 M, 16 TTH, 15 M + TTH. Headache recorded daily during pregnancy and 3 months post-partum
Granella et al. [11]	R	200	76.8	22.2	1	100 MA and 200 MO as controls
Mattsson [12]	R	728	81.4	17.6	1	Full sample size: 728; full information available for 102 women
Sances et al. [13]	P	47	87.2	12.8	0	Full sample size 49: 2 MA, 47 MO
Kelman [14]	R	504	38.2	27.8	34	Greater improvement in MO patients rather than MA patients
Ertresvåg et al. [15]	P	410	65.9	19.8	14.4	Full sample size: 1361 women. 410 with M.
Melhado et al. [16]	P	737	65	26.1	8.9	Full sample size: 1101 women. 737 with M. Data partially derived from graphics
Summary		3346	66.9	25.8	8	
Migraine with aura						
Maggioni et al. [5]	R	12	83.4	16.6	0	430 women 3 days after delivery; among them, 81 MO, 12 MA, 33 TTH
Granella et al. [11]	R	100	43.6	48.7	7.7	100 MA and 200 MO as controls
Mattsson [12]	R	728	78.3	4.3	17.4	Full sample size: 728; full information available for 23 women
Summary		840	68.4	23.2	8.4	
Tension-type Headache						
Maggioni et al. [5]	R	33	82,1	17,9	0	Full sample size: 430 women, interviewed 3 days after delivery; among them, 81 MO, 12 MA, 33 TTH
Melhado et al. [16]	P	112	N/A (≈ 60)	N/A (≈ 35)	N/A (≈ 5)	Full sample size: 1101 women. 112 with TTH. Data derived from graphics
Summary		145	–	–	–	
Cluster Headache						
Van Vliet et al. [31]	R	53	69,9	20,7	9,4	Full sample size: 196 CH; 53 had their first attack before the first pregnancy. 23% of episodic CH patients reported that an "expected" cluster period did not occur during pregnancy. Here improvement includes 8 patients who had a cluster period within 1 month after delivery.

M, migraine; *MO*, migraine without aura; *MA*, migraine with aura; *TTH*, tension type headache; *CH*, cluster headache

pregnancy are more common among pregnant women with migrainous headache than in those without headache or with non-migrainous headache [15].

Postpartum headache occurs in about 30–40% of all women, not only migraineurs [6, 9, 13]. Most of the attacks develop during the first week after delivery, with apparent sparing of the day of birth. During puerperium mean headache intensity, pain duration and analgesic therapies increase, as confirmed by a large prospective trial [17]. On the other side, the MIGRA study showed a decline in attacks frequency starting five weeks after delivery [17]. None of the migraineurs experiencing a complete pain remission during the first or the second trimester should experience a recurrence of migraine attacks before delivery [13], even if a study reported an increase in headache burden already in the four weeks before birth in multiparous women, defining a U-shaped curve to describe migraine evolution during pregnancy [9]. A large multicentre study set at 3.7% the amount of women experiencing headache within 72 h after delivery, identifying headache during pregnancy and regional anaesthesia injections as risk factors [28]. Migraine usually returns quickly after delivery, probably triggered by the abrupt fall in the level of estrogens, by a postpartum depression or because of the new parental role and all that it implies (sleep deprivation, anxiety, worry and psychological adaptation). Pre-pregnancy headache pattern restores within 1 month from delivery in 55% of patients and only breast-feeding and age > 30 years have been reported to retard headache recurrence [13]. Migraine recurred within the first post-partum month in 100% of women who bottle-fed and in only 43.2% of those who breastfed [13]. However, other studies found no significant association between headache improvement from the second trimester to the postpartum and breastfeeding [10, 17].

At present only one study dealt with the headache attacks during the course of in vitro fertilization and embryo-transfer treatments [29]. The prevalence of headache attacks is higher at the first stage of the procedure (with gnrh analogue administration) and at the end of the treatment protocol in cases there is no conception, in both situations because of a decline in blood levels of estrogens.

Tension-type headache

TTH represents 26% of headaches in pregnancy [30]. TTH would be expected to improve during gestation as female hormones modulate serotonin and endorphins, which are involved in TTH pathophysiology [4]. Actually, 17.9% of TTH patients reported no change in the headache burden during pregnancy (Table 1), with worsening in 5% of cases and improvement in a quarter of women [3, 30]. A study found significantly higher remission and improvement rates than in MO (Table 1) [5]. Whatever if women with TTH showed a great or a modest improvement, this is usually reported as marked as for the migraineurs [10, 16]. On the contrary, TTH rarely worsens during gestation [16] and, according to some Authors, it never does [5].

Cluster headache

Cluster headache (CH) is a relatively rare primary headache, severe in intensity, stabbing in quality, highly debilitating, associated with autonomic symptoms and affecting men more frequently than women. Scientific literature lacks of large prospective studies about the effect of pregnancy on CH, as it is seen in less than 0.3% of pregnancies [30]. Despite the rare cases in which the first attacks occur during the first pregnancy, almost a quarter of pregnant women report that an expected cluster period does not develop during gestation while it may start soon after delivery [31]. Otherwise, CH attacks do not change in intensity and frequency in the majority of cases. As a consequence, women who have their first attack before their first gestation usually have fewer children than those who already were mother at the time of clinical onset; this is probably due to the prospective of the treatment limitations in case of CH during pregnancy [31].

Secondary headaches

Pregnancy is a risk factor for a secondary headache disorder. Hypercoagulability, hormonal changes and anaesthesia for labour are just some of the multiple factors contributing to the high incidence of secondary headaches during pregnancy.

A recent study by Robbins et al. Found 35% of secondary headaches among 140 pregnant women presenting with acute headache: hypertensive disorders of pregnancy covered 51% of these cases (about 18% of total), with pre-eclampsia as the major cause, followed by reversible posterior leukoencephalopathy syndrome (PRES, eclampsia), reversible cerebral vasoconstriction syndrome (RCVS) and acute arterial hypertension [32]. These data place between two previous studies that reported percentages of secondary headaches ranging from 14.3% to 52.6% [16, 33]. In particular, among patients with a primary headache history, longer attack duration is the most common feature suggesting a secondary headache, reaching the statistical significance [32] or just approaching it [33].

The authors show how lack of headache history, elevated blood pressure and abnormalities at neurologic examination are the main red flags for a secondary origin of an acute headache during pregnancy [32]. In the second trimester, a new onset of headache may signal the presence of a pseudotumor cerebri [34], while in case of a severe postural headache a spontaneous intracranial hypotension must be ruled out [35]. In front of the well-known red flags (Table 2) brain MRI or CT scan are often required [30, 36].

Table 2 Red Flags for headache in pregnancy

1.	Headache that peaks in severity in less than five minutes
2.	New headache type versus a worsening of a previous headache
3.	Change in previously stable headache pattern
4.	Headache that changes with posture (e.g. Standing up)
5.	Headache awakening the pregnant
6.	Headache precipitated by physical activity or Valsalva manoeuvre (e.g. Coughing, laughing, straining)
7.	Thrombophilia
8.	Neurological symptoms or signs
9.	Trauma
10.	Fever
11.	Seizures
12.	History of malignancy
13.	History of HIV or active infections
14.	History of pituitary disorders
15.	Elevated blood pressure
16.	Recent travel at risk of infective disease

Modified from Mitsikostas et al. 2015 [38] (European Headache Federation consensus on technical investigation for primary headache disorders)

Use of contrast agents such as gadolinium is not recommended, given the lack of data regarding safety to the fetus and its ability to cross the placenta and remain in the amniotic fluid [30].

Iodinated contrast should be avoided as well as it may suppress fetal thyroid function [37].

Recently the European Headache Federation (EHF) published a consensus statement on technical investigation for primary headache disorders [38].

Secondary headache features may not differ from those of primary headaches; furthermore, migraine is as an independent risk factor for the development of secondary headaches (e.g., the risk of gestational hypertension increased by 1.42-fold with an OR of 2.3 (CI 2.1–2.5) [39], so that recognizing these conditions in pregnant women may be a true diagnostic challenge.

Cerebral venous thrombosis (CVT), pre-eclampsia, haemorrhagic or ischemic stroke, subarachnoid haemorrhage (SAH), RCVS, PRES, idiopathic intracranial hypertension (IIH) or pituitary apoplexy must be ruled out as soon as possible (Table 3) [3, 37].

Cerebral venous thrombosis

Headache caused by CVT has no specific characteristics: it is most often diffuse, progressive and severe, but can be unilateral and sudden (even thunderclap), or mild, and sometimes is migraine-like [40]. Headache is present in 80–90% of cases of CVT and it is often associated with focal signs (neurological deficits or seizures) and/or signs of intracranial hypertension (nausea and papilledema),

Table 3 Main causes of secondary headache in pregnant women

Secondary headaches during pregnancy	
Arterial dissection	Intracranial hypotension
Arteriovenous malformation	Ischemic stroke
Brain tumors	Meningitis/encephalitis
Cerebral venous thrombosis (CVT)	Pituitary adenoma
Choriocarcinoma	Pituitary apoplexy
Cranial neuralgias	Pituitary meningioma
Dehydration	Reversible posterior leukoencephalopathy syndrome (PRES)
Eclampsia and pre-eclampsia	Reversible vasoconstriction syndrome (RCVS)
Head trauma	Sinusitis
Idiopathic intracranial hypertension (IIH)	Subarachnoid haemorrhage (SAH)
Intracranial haemorrhage (ICH)	Vasculitis

subacute encephalopathy or cavernous sinus syndrome, carrying a mortality rate of up to 30% [30].

Pre-eclampsia and eclampsia

Pre-eclampsia occurs in 5% of pregnancies [30]: a progressive bilateral (temporal, frontal, occipital or diffuse) pulsating headache in a woman who is pregnant or in the puerperium (up to 4 weeks postpartum), often aggravated by physical activity, failing to respond to the over-the-counter remedies, may be the herald symptom of this condition, which can associate with visual changes similar to the typical visual aura. It must resolve within a week after blood pressure adjustment [4, 41]. According to the International Classification of Headache Disorders (ICHD-3beta) headache should have at least two of the following three characteristics: a) bilateral location, b) pulsating quality, and c) aggravated by physical activity [42].

Ischaemic stroke

Headache accompanies ischaemic stroke especially within the posterior circulation, in up to one-third of cases and is usually overshadowed by focal signs and/or alterations of consciousness, which in most cases allows easy differentiation from the primary headaches. The risk of ischaemic stroke in migraineurs was evaluated using the United States (US) Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality and found to be elevated [39].

Headache has a self-limited course, and is very rarely the presenting or a prominent feature of ischaemic stroke [43]. It is usually of moderate intensity, and has no specific characteristics. It can be bilateral or unilateral ipsilateral to the stroke. Rarely, an acute ischaemic stroke can present with an isolated sudden (even thunderclap) headache [44].

The diagnosis of headache and its causal link with ischaemic stroke is easy because the headache presents both acutely and with neurological signs and because it often remits rapidly.

Subarachnoid haemorrhage

In SAH headache is usually the prominent symptom. The pain is typically severe and sudden, peaking in seconds (thunderclap headache) or minutes, often followed by vomiting and loss of consciousness [45]. SAH is a serious condition with mortality rate of 40–50% and with 10–20% of patients dying before arriving at hospital. The abrupt onset is the key feature and can help to distinguish from primary headaches with thunderclap features (e.g., associated with exercise or sexual activity). SAH presents a 20-fold increased risk in the puerperium and it gives a thunderclap headache [30].

Arterial dissection

Arterial dissection is a rare complication of pregnancy and puerperium. There have been reports of cervical carotid, vertebral and intracranial artery dissection in association with preeclampsia [46]. Headache is the most frequent inaugural symptom, described as severe, unilateral (ipsilateral to the dissected vessel), with a sudden (even thunderclap) onset. Pain is persistent for days and can remain isolated or be a warning symptom preceding ischaemic infarcts.

Reversible cerebral vasoconstriction syndrome

Headache caused by RCVS syndrome is severe and diffuse and typically of the thunderclap type, recurring over 1–2 weeks, often triggered by sexual activity, exertion, Valsalva manoeuvres and/or emotion [47]. Headache is often the only symptom of RCVS, but the condition can be associated with fluctuating focal neurological deficits and sometimes seizures.

RCVS is commonly associated with the post-partum period, usually within a week after delivery: its severe thunderclap headache usually relapses within a few days, resolving by approximately twelve weeks after clinical onset [21, 37]. The typical differential diagnosis is cerebral vasculitis, which needs to be ruled out due to the course of the disease and different treatment options.

Posterior reversible encephalopathy syndrome

PRES is a neuro-radiological clinical entity characterized by insidious onset of headache, impaired consciousness, visual changes or blindness, seizures, nausea, and vomiting, and focal neurological signs. In nearly 2/3 of patients with PRES, headache is the most common symptom and is usually described as occipital and bilateral and dull in nature [48]. Symptoms develop without prodrome, and progress over 12–48 h.

PRES is often associated with hypertensive encephalopathy, preeclampsia, eclampsia, RCVS, renal failure, immunosuppressive therapy or chemotherapy. PRES is more common in women and the development of this condition after delivery is unusual. The condition is usually reversible when early diagnosis is established and appropriate treatment is started without delay; symptoms generally resolve within a period of days or weeks while recovery of the MRI abnormalities takes longer [49].

Idiopathic intracranial hypertension

Usually during the first trimester, obese women can suffer from a progressive, daily headache, aggravated by Valsalva and position change, associated with papilledema and severe visual deficits, together with tinnitus or sixth-nerve palsies, defining the clinical pattern of IIH [30, 37, 50]. The headache is frequently described as frontal, retro-orbital, 'pressure like' or explosive; migraine-like headache may also occur.

Pituitary apoplexy

Pituitary apoplexy is a rare cause of sudden and severe headache during pregnancy [51]. The sudden rise of a severe headache, with nausea, vomiting, ophtalmoplegia, altered consciousness and accompanied from onset or later by visual symptoms and/or hypopituitarism must raise the clinical suspicion of a pituitary apoplexy [4, 50]. The rare clinical syndrome of pituitary apoplexy is an acute, life-threatening condition. It is important to distinguish from the other causes of thunderclap headache [52]. Most cases occur as the first presentation of rapid enlargement of non-functioning pituitary macroadenomas as a result of haemorrhage and/or infarction.

Treatment of headaches in pregnancy and breastfeeding women

During pregnancy, inadvertent exposure to teratogenic agents can lead to irreversible fetal malformations [53, 54]. Unfortunately, most patients are not aware of possible teratogenic risks of used medications and their safety profiles during pregnancy [55].

During pregnancy and breastfeeding the preferred therapeutic strategy should always be a non-pharmacological one. Nevertheless, an undermanaged headache can lead to stress, sleep deprivation, depression and poor nutritional intake which in turn can have negative consequences for mother and baby. Therefore, if non-pharmacological interventions seem inadequate, a well-considered choice should be made concerning the use of medication, taking into account all the benefits and possible risks (Tables 4 and 5). A basic rule should be to aim for the lowest effective dose and the shortest duration of treatment.

Medication is considered safe during breastfeeding if the relative infant dose is <10% [36, 56]. The risk of adverse

Table 4 Summarizing table on treatment of headache in pregnant women

Medication	Adverse effects	Concerns	Comments
Paracetamol	–	Possible increased risk for asthma, ADHD	Preferred acute treatment
Nsaids (non-selective): ibuprofen, naproxen, diclofenac, indomethacin	- TR1: miscarriage - TR3: premature closure ductus arteriosus, impaired renal function, cerebral palsy, intraventricular haemorrhage	TR1: possible associated CM	- can be used safely during TR2 - avoid in TR3 - selective COX-inhibitors contra-indicated
Triptans: sumatriptan, zolmitriptan, eletriptan, rizatriptan	No major congenital defects	TR1: possible link with behavioral problems	Appropriate if benefit outweighs risk
Aspirin (ASA)	> 100 mg/d or TR3: premature closure of ductus arteriosus, oligohydramnios, neonatal bleeding	–	- < 100 mg/day seems safe - caution in TR1 and TR2 - avoid in TR3
Caffeine	–	Moderate to high daily doses: possible association with miscarriage, low birth weight, preterm delivery	–
Combined preparations: paracetamol, aspirin and caffeine	–	–	Not recommended
High flow oxygen	–	–	Preferred acute treatment in CH
Lidocaine	–	–	- second line acute treatment in CH - intranasal formulation preferred
Corticosteroids: prednisone, prednisolone	–	Possible early lung maturation	- avoid during first semester - low doses recommended - reserved for CH or status migrainosus
Weak opioids: tramadol, codeine	- MOH - withdrawal symptoms and respiratory depression in the newborn	–	- not considered first line treatment in primary headaches - caution in TR1 and TR2 - avoid in TR3
Ergots/Ergots Alkaloids	- uterotonic and vasoconstrictive effect - fetal distress - CM	–	Avoid in any trimester
B-blockers: metoprolol, propranolol	Neonatal bradycardia, hypotension, hypoglycaemia when exposed in TR3	- intrauterine growth retardation - preterm birth - respiratory distress	- first line migraine prophylaxis - if possible tapper off TR3 - monitor newborn exposed in TR3
ACE- I, ARB	CM	–	Avoid in any trimester
Verapamil	–	–	First line CH profylaxis
TCA	–	- possible CM (not confirmed) - withdrawal symptoms in the newborn	- second line migraine prophyaxis when β-blocker ineffective/contra-indicated - amytriptiline preferred
Venlafaxine	CM	–	Should be avoided
Duloxetine	–	–	No reported AE

Table 4 Summarizing table on treatment of headache in pregnant women *(Continued)*

Medication	Adverse effects	Concerns	Comments
Valproate	Neural tube defects, cardiac defects, urinary tract defects, cleft palate, lower IQ scores	–	Avoid in any trimester
Topiramate	Cleft lip/palate, low birth weight	–	Avoid in any trimester
Gabapentin	–	Osteological deformities	Limited data
Lamotrigine	No major congenital defects	Increased occurrence of autism/dyspraxia	Safest antiepileptic drug
Magnesium	- high dose I.V.: bone abnormalities - possible transient neurological symptoms and hypotonia after delivery	Possible bone abnormalities in lower dosage or when taken orally	- appropriate in any trimester; caution directly before delivery - chronic use of oral magnesium: controversial
Coenzyme Q10	–	–	No reported AE
Feverfew, butterbur, high dosed riboflavine	–	Possible CM	Not recommended
Flunarizine	–	–	Not recommended (no data available)
Lithium	- congenital cardiac malformations and cardiac arrhythmias - anomalies of the CNS and endocrine system - polyhydramnios - stillbirth	–	Not recommended but can be considered in uncontrolled CH refractory to Verapamil
Botulinum toxin A	–	–	No reported AE when injected correctly
Nerve blocks	–	–	- no reported AE when injected correctly - preferred agent: lidocaine

Adverse effects are the known proven side effects. Concerns cover issues that are presumed based on limited data but for which the causal relationship is not clear
TR1, first trimester; *TR2*, second trimester; *TR3*, third trimestes; *AE*, adverse effects; *ADHD*, attention-deficit/hyperactivity disorder; *CM*, congenital malformation; *CH*: cluster headache, *TCA*, tricyclic antidepressants; *ACE-I*, ACE-inhibitor; *ARB*, angiotensin-receptor blocker; *I.V.*, intravenously

Table 5 Summarizing table on treatment of headache in breatsfeeding women

Medication	Adverse effects	Comments
Paracetamol	–	Preferred acute treatment
Nsaids (Non-selective): Ibuprofen, naproxen, indomethacin	Aggravation of jaundice	Ibuprofen preferred
Triptans	–	- sumatriptan: no need to 'pump and dump' - less evidence on the other triptans: avoid nursing for 24 h after use of triptan as extra safety measurement
Aspirin (ASA)	Reye's syndrome	Not recommended
Caffeine	–	Moderate dosage
High flow oxygen	–	Preferred acute treatment in CH
Lidocaine	–	- second line acute treatment in CH - intranasal formulation preferred
Corticosteroids: prednisone, prednisolone	Prolonged high-dosed therapy: infant growth and development can be affected	Intravenously: delay breastfeeding for 2-8 h
Weak opioids: tramadol, codeine	Sedation and respiratory depression in the infant	Not considered first line treatment in primary headaches
Ergots/Ergots Alkaloids	- vomiting, diarrhea, convulsions - decrease of prolactine in the mother	Avoid in any trimester
B-blockers: metoprolol, propranolol	- hypotension, bradycardia - weakness	- metoprolol preferred - avoid in children with astma
ACE-I, ARB	Impact on kidney development	Probably compatible (limited data)
Verapamil	–	First line CH profylaxis
TCA	–	No reported AE
Venlafaxine	–	No reported AE
Duloxetine	–	No reported AE
Valproate	Interfere with liver and platelet function	Avoid in women of child-bearing age
Topiramate	- sedation, irritability - poor suckling, diarrhea	–
Gabapentin	–	No reported AE
Lamotrigine	–	No reported AE
Magnesium, Riboflavine	–	No reported AE
Flunarizine	–	Not recommended: no data available
Lithium	Renal toxicity	Not recommended, but can be considered in uncontrolled CH, refractory to Verapamil
Botox	–	No reported AE when injected correctly
Nerve blocks	–	No reported AE when injected correctly

Adverse effects are the known proven side effects. Concerns cover issues that are presumed based on limited data but for which the causal relationship is not clear

TR1, first trimester; *TR2*, second trimester; *TR3*, third trimestes; *AE*, adverse effects; *ADHD*, attention-deficit/hyperactivity disorder; *CM*, congenital malformation; *CH*: cluster headache, *TCA*, tricyclic antidepressants; *ACE-I*, ACE-inhibitor; *ARB*, angiotensin-receptor blocker; *I.V.*, intravenously

events could be minimized by taking medication directly after breastfeeding and discarding all milk for at least 4 h [18].

Non-pharmacological treatment

Triggers like sleep deprivation, skipping meals and emotional stress should be avoided. A balanced lifestyle with attention for physical activity and regular eating and sleeping habits is recommended [37, 57–62]. Acupuncture and behavioral therapies like biofeeback and yoga can be helpfull [37, 58, 62]. In particular for women with CH screening for sleep apnea is usefull, since prevelance seems higher in cluster patients and in pregnancy [63]. Treatment with a dental device or continuous positive airway pressure can be proposed [57].

Symptomatic treatment

Paracetamol/acetaminophen

Paracetamol is considered the safest option to treat acute pain during pregnancy and breastfeeding [37, 50, 54, 59–62, 64, 65]. Despite this historical reputation, new data suggesting a possible relationship between prenatal exposure to paracetamol and an increased risk of asthma and attention-deficit/hyperactivity disorder (ADHD) in the child raise some concern [37, 60, 62]. Patients should be educated about the difference between paracetamol and combinated drugs containing paracetamol and other substances, like codeine or caffeine.

Aspirin

The use of acetylsalicylic acid (ASA) in low doses (< 100 mg/day) does not seem to induce any associated maternal or neonatal complications. However, higher doses should be avoided as well as its use in the third trimester, since there might be a link with premature closure of the ductus arteriosus and oligohydramnios [20, 50, 53, 54, 60]. Due to its effect on platelet function, ASA can also increase the risk of neonatal bleeding [18].

Breastfeeding women should be discouraged to use ASA due to a potential toxicity. It is associated with Reye's syndrome. A potential adverse effect on platelet function in the infant is suspected, but remains unclear [37, 59, 61, 64].

Caffeine

In animal studies a teratogenic effect of high-dosed caffeine was demonstrated. On the other hand, caffeine-containing beverages are consumed very commonly during pregnancy, without any reported adverse effect. In general the use of caffeine in low doses is assumed to be safe. Moderate-to-high daily doses are more controversial since they might be associated with miscarriage, low birth weight and preterm delivery [60, 62, 66]. Combined preparations containing paracetamol, aspirin and caffeine should be avoided [50].

Moderate intake of caffeine seems safe for mother and child when breastfeeding [64].

Non-steroidal anti-inflammatory drugs

Attention should be paid to the timing of the pregnancy and the type of non-steroidal anti-inflammatory drugs (nsaids) used. Non-selective COX-inhibitors like ibuprofen, naproxen and diclofenac can be a relative safe choice in the second trimester. Nsaids are not recommended in the third trimester since there is an increased risk of complications like premature closure of the ductus arteriosus, impaired renal function, cerebral palsy and neonatal intraventricular haemorrhage [50, 61, 62, 66]. More recent data suggest to avoid nsaids during the first trimester as well. An increased risk of miscarriage is suspected when used close to conception based on available reports and seems plausible regarding the pharmacological properties of this drug. Different studies covering over 20.000 pregnancies reported on the association between congenital malformation and prenatal nsaids exposure in the first trimester. Some population-based studies confirm the association, but others do not [37, 60, 61]. Selective COX2-inhibitors are contraindicated in pregnancy based on the few prenatal data available [60].

Naproxen, indomethacin and ibuprofen are compatible with breastfeeding, prefering ibuprofen because of its short elimination half-life and low excretion in human milk. In newborns with jaundice nsaids exposure can exacerbate the condition [37, 60, 61, 64].

Triptans

Considerable data is available on the use of sumatriptan in pregnancy. A few large pregnancy registries covering more than 3000 pregnancies, retrospectively analyse the use of other triptans, in particular rizatriptan, zolmitriptan and eletriptan [37, 56]. Due to its small molecular weight, sumatriptan can pass through the placenta [67]. However, the transfer is slow and passive, so that only about 15% of maternal dose reach the fetus after 4 h [68]. Ephross et al. Reported the last data from the sumatriptan and naratriptan pregnancy registries [69]. Until 2012, the registry included 680 exposed women, giving birth to 689 fetuses. 90.9% of them were exposed to sumatriptan. The overall risk of major birth defects under sumatriptan exposure was 4.2%. The most common birth defects were ventricular septal defect (n = 4), pyloric stenosis (n = 3) and chromosomal abnormalities (n = 5). The authors concluded that sumatriptan does not lead to teratogenity, as risk rates for major birth defects were similar to general population (3–5%). Only one major birth defect, i.e. Ventricular septal defect, occurred under naratriptan exposure during first trimester in a fetus who was also exposed to sumatriptan. The number of newborns exposed to naratriptan was too low to allow accurate interpretation [69]. In the rizatriptan registry 4 major birth malformations occurred in 56 pregnancies (7.1%). Also in this case data are currently too scarce to draw any conclusion [56, 70]. Observational studies conducted in Denmark, Sweden and Norway reported no increased risk for fetal malformations under triptan use [67, 71–73]. However, children exposed to triptans in utero might have a higher risk of developing externalizing behaviors [74]. Exposure to triptans in late pregnancy is associated with an increased risk of atonic uterus and postpartum haemorrhage [37, 56, 60, 61, 69, 72, 73, 75, 76]. In their meta-analysis, Marchenko et al. Concluded that triptans do not lead to increased rates of major congenital malformations [76]. The rates of spontaneous abortions were elevated when compared to healthy controls (OR 3.54), but not with untreated migraineurs [76]. Entries in pregnancy registries are voluntary and therefore not systematic. Most registers and observational studies do not

include sufficient data about how often triptans were taken, exposure to concomitant medications or severity of illness as a possible confounders [76–78]. Some concern exists on a potential increased risk of behavioral problems like attention deficit and aggression disorders after prenatal exposure to triptans, in particular in the first trimester [74].

The use of sumatriptan is compatible with breastfeeding without the need to "pump and dump". The infant exposure is very low corresponding to 0.5% of maternal dose and no adverse events on the nursing infant were reported [77]. Theoretically, eletriptan can be considered even safer as the dose in breast milk is only 0.002% after 24 h [36]. Clear controlled evidence on the other triptans is lacking. They are considered probably compatible with breastfeeding [37, 57, 59, 61, 62, 64, 79]. As an extra safety measure it can be advised to avoid breastfeeding for 24 h after their use [59].

Oxygen

In pregnant and breastfeeding women with CH, high flow oxygen administered via a non-rebreathing mask is the preferred treatment. It seems a safe option without proven adverse effect on the child or the mother [50, 57, 79, 80].

Lidocaine

The use of lidocaine is a considerable option for pregnant women with CH, when treatment with oxygen is insufficient [50, 57, 80]. The intranasal formulation is preferred since it is presumed to have a better safety profile than the systemic formulations [80].

Lidocaine is compatible with breastfeeding in any formulation [57, 64, 79, 80].

Corticosteroids

There is some concern about early lung maturation and a slightly increased risk for cleft palate, but in disabilitating CH and status migrainosus prednisone and prednisolone remain a reasonable alternative [57, 60, 65, 80]. Therefore, they should be avoided during first trimester and the dose should be kept as low as possible [80].

Oral prednisone and prednisolone are compatible with breastfeeding as only about 1–2% of the mother dose transfers to the fetus [64]. Prolonged high-dosed therapy should be avoided since infant growth and development could be affected [57, 64]. When administered intravenously, breastfeeding should be delayed untill 2 to 8 h after administration [80].

Opioids

Weak opioids like tramadol and codeine can be considered when non-opioid medication brings no relief [37, 61, 66, 81]. Codeine was initially supposed to increase the risk for cleft palate and inguinal hernia but large observational studies could not confirm it [81]. A slightly higher risk for cardiac defects or spina bifida has been described after opioid exposure in first trimester [61]. Prolonged use of such drugs should be clearly discouraged because of the risk of medication overuse headache (MOH) for the mother and dependency with withdrawal syndrome in the newborn [37, 62]. Stronger formulations should be used with caution and opioid use is discouraged during third trimester, since narcotics cross the placenta and can cause fetal bradycardia, respiratory depression and birth defects [61, 62].

Sporadic use of weak opioids is compatible with breastfeeding. When repeated dosing or highly dosed opioids are needed, there is a risk of sedation, respiratory depression and constipation in the infant [37, 61, 64].

Ergots and ergots alkaloids

Ergots and ergots alkaloids are contraindicated in pregnancy due to a known uterotonic and vasoconstrictive effect as well as a range of serious adverse effects on the fetus like fetal distress and birth defects [18, 37, 50, 57, 59, 61, 62, 66]. Other possible teratogenic effects include intestinal atresia and poor cerebral development [3].

They should be avoided in nursing women. Beside systemic side effects in the infant like vomiting, diarrhea and convulsions, prolactine can be decreased by these drugs, reducing the milk production [37, 59, 61, 64].

Antiemetics

Antiemetics are believed to be mostly safe during pregnancy [21]. However, only little data are available.

Metoclopramide is commonly used during pregnancy without significant fetal side effects [50, 54, 57, 59, 61, 62]. Chlorpromazine and prochlorperazine could have an increased risk for neonatal extrapyramidal or withdrawal symptoms if taken during third trimester [37], domperidon might lead to long QT syndrome [82], and under diphenhydramin, sedation and apnea after delivery are possible [64].

Doxylamine, histamine H1 receptor antagonists, pyridoxine, dicycloverine and phenothiazines are other options without noted adverse pregnancy outcomes [54]. Recently some concerns arised on the use of ondansetron during pregnancy. There seems to be conflicting evidence about a possible teratogenic effect as well as the potential to cause a serotonin syndrome and QT prolongation [37].

A potential toxicity of metaclopramide, chlorpromazine and prochlorperazine for the infant is suspected when used in nursing mothers [57, 59, 64]. Antiemetics could lead to sedation or irritability, but also apnea and extrapyramidal symptoms are possible [37].

Based on the above mentioned informations paracetamol 500 mg alone or in combination with aspirin 100 mg, metoclopramide 10 mg, or tramadol 50 mg are recommended as first choice symptomatic treatment of a

moderate-to-severe primary headache during pregrancy. Sumatriptan may be the second choice symptomatic treatment for migraine in pregnant women.

Preventative treatment

Antihypertensive drugs

B-blockers (metoprolol and propranolol) are the first line option as migraine prophylaxis in pregnant and breastfeeding women. [37, 54, 59–61]. Potential fetal side effects like intrauterine growth retardation, preterm birth and respiratory distress are described in some studies [37, 60]. If possible a prelabour tapper off should be achieved as the use of β-blockers in the third trimester can induce neonatal pharmacological effects like bradycardia, hypotension and hypoglycaemia. Newborns exposed in the last trimester should be closely monitored [37, 61].

B-blockers are excreted in breast milk in very low doses and infant plasma concentrations are negligible. When nursing, metoprolol is preferred over propranolol. Possible side effects include drowsiness, neonatal hypoglycemia, hypotension, weakness and bradycardia [37]. Caution has to be paid in infants with astma [64].

Antihypertensive drugs which interfere with the renine-angiotensine system, like the ACE inhibitor lisinopril or the angiotensin-receptor blocker candesartan, are considered contraindicated at any stage of pregnancy since their use involves a significant fetal risk [37, 61]. Candesartan is probably compatible with breastfeeding with special attention for kidney development [64]. Lisinopril seems probably compatible as well, but there is no specific breastfeeding data available [64].

When prophylactic treatment is needed in a pregnant or breastfeeding CH patient, verapamil in the lowest effective dose remains the first choice [57, 64, 79, 80].

Antidepressants

The tricyclic antidepressants (TCA) are considered the safest second-line option when β-blockers are contraindicated or ineffective. Amitriptyline is preferred. Some studies suggest a possible teratogenic effect of TCA (e.g., cardiovascular or limb abnormalities), but a clear causal relationship can not be proven [18, 37, 59, 61, 62]. If used late in pregnancy, all antidepressants might lead to withdrawal symptoms [82]. Amitriptyline and nortriptyline are relatively safe during breastfeeding. In mothers treated with amitriptylin, infants are exposed to about 1–2% of maternal dose and no accumulation is supposed [60] and this does not seem to have a negative impact on the child [59–61, 64]. However, drowsiness and anticholinergic symptoms like dry mouth or constipation might occur [37].

The seretonin norepinephrine reuptake inhibitor (SNRI) venlafaxine should be avoided during pregnancy. There is no clear indication of a possible teratogenic or abortifacient effect of duloxetine. No adverse pediatric effects have been reported in the little data on nursing infants of mothers using the snris duloxetine and venlafaxine [50, 60, 62, 64].

Antiepileptic drugs

Valproate is contraindicated during pregnancy because of devastating fetal side-effects like neural tube defects and other major malformations such as cleft palate, cardiac or urinary tract defects [37, 54, 61, 83]. Valproate transfers to breast milk in very low doses and is unlikely to affect the child seriously [37]. Although valproate seems safe when breastfeeding, it should be avoided in women of childbearing age because of its teratogenic effect. When nursing on valproate can not be avoided, monitoring for liver and platelet function in the child is advised [59, 61, 64].

The use of topiramate in pregnancy is associated with an increased risk of cleft lip/palate and low birth weight, especially when taken during first trimester [81]. The possible benefits as a migraine prevention do not seem to outweigh the risks. Therefore topiramate should be avoided in this context [37, 54, 60, 62, 84]. Topiramate reaches infant plasma level up to 25% of maternal levels and newborns should be monitored for sedation, irritability, poor suckling, weight loss and diarrhea. No other significant side effects have been reported [61, 64, 84].

Data on prenatal exposure to gabapentin are limited. A link with osteological deformities is suspected. Therefore, its use is not recommended during pregnancy [54, 60]. Gabapentin seems compatible with breastfeeding. No special concerns were reported to date [64].

Lamotrigine has a good safety profile compared with other antiepileptic drugs, therefore, it is the preferred option for women of child-bearing age. A recent meta-analyses found that rates of miscarriages, stillbirths, preterm deliveries, and small for gestational age neonates are not increased after in-utero exposure to lamotrigine compared to the general population [85]. Similarly, in-utero exposure to lamotrigine does not seem associated with increased rates of inborn defects and long-term neurodevelopmental damage [85].

The treatment with lamotrigine during breastfeeding is safe and no serious adverse effects or cognitive and development alterations have been reported [86].

Dietary supplements

Magnesium (up to 350 mg/die) can be used during pregnancy [81]. However, transient neurological symptoms in newborns and hypotonia have been reported [82]. If magnesium is administered intravenously over a long time, bone abnormalities are possible [37]. Due to these findings chronic use of magnesium during pregnancy seems more controversial now than before [37, 62].

Coenzyme Q10 seems a reasonable option for preventative treatment while pregnant. Up to date there are no severe adverse events reported [37, 58].

Feverfew (*Tanacetum parthenium*), butterbur (*Petasites hybridus*) and high dosed riboflavine are not recommended during pregnancy [37, 61].

Both magnesium and riboflavine are compatible with breastfeeding. About the safety of coenzyme Q10, feverfew and butterbur in lactation no clear information is available [61, 64].

Flunarizine

Calcium channel blockers should be avoided in pregnancy and breastfeeding, since there are not enough safety data [37, 54, 61].

Lithium

Lithium in CH should generally not be used in pregnancy because of a known teratogenic effect. It is associated with congenital cardiac malformations and cardiac arrhythmias, anomalies of the central nervous sytem and endocrine system, polyhydramnios and stillbirth. Use of lithium can be considered in pregnant severe CH patients when verapamil is ineffective, if the benefit to the mother clearly exceeds the possible risk to the fetus [57, 62, 79, 80].

Lithium reaches a high relative infant dose of 50%. Mainly the kindney in newborns seems sensitive to lithium and renal toxicity is described [57].

Prescription of lithium in lactating women is controversial but as in pregnant women, in cases of severe uncontrolled CH it can be considered [57, 79].

Botulinum toxin type a

Botulinum toxin type A is probably safe during pregnancy due to its local mechanisms of action. However, only very few data are available and mainly for its use as cosmetic treatment [61].

There are no reports for botulinum toxin type A during breast-feeding but a transfer to breast milk is not probable due to its high molecular weight [61].

As no well-controlled data is available for his indication for now it should only be reserved for severe treatment-refractory chronic migraine patients [37, 61, 87].

Nerve blocks

Periferal nerve blocks are considered safe in pregnancy and breastfeeding. Due to their periferal localization, the systemic effect is considerably smaller than in oral medication. The preferred agent to inject is lidocaine. Alternatives are bupivacaine or betamethasone. Bupivacaine may be associated with fetal cardiotoxicity [37, 57, 62, 88, 89].

Melatonin

There is no clear evidence of harmfull adverse events when using melatonin during pregnancy. However it is suggested that administration of exogenous melatonin during pregnancy can interfere with the development of the postnatal circadian rhythm [79].

Melatonin is a natural substance of breastmilk and is excreted in a circadian cycle. Hypotheticaly the use of exogenous melatonin can be thought to have a negative influence on postnatal sleep patterns and other hormonal cycles. There is no relevant data available to support this hypothesis [79]. Melatonin in low doses seems compatible with breastfeeding [64].

Headache-related complications during pregnancy

Headache during pregnancy requires particular attention because it can be a symptom of secondary conditions, including CVT, hypertensive disorders, stroke and pituitary apoplexy [50]. At the same time, preexisting primary headache conditions can influence the course of pregnancy and delivery, and lead to a higher risk of complications [18].

Pregnancy complication in migraine patients

Most previous literature focused on the effects of migraine on pregnancy, while other headache disorders were often neglected. In general, a preexisting migraine does not represent a risk factor for negative pregnancy outcome and no increase rate of fetal malformations could be detected in pregnant women suffering from migraine [3, 41]. However, migraine can be considered an important risk factor for hypertensive and vascular diseases during pregnancy [90].

The largest study to investigate the relationship between migraine and pregnancy complications was conducted by Bushnell et al. In form of a retrospective, population based case-control study on 18,345,538 pregnancies in the United States between 2000 and 2003 [91]. 33,956 (0.2%) of the examined pregnant women had a migraine diagnosis. The authors detected a strong correlation between migraine and vascular diseases. In particular, the risk for stroke was 15-fold higher, with odds ratios of 30.7 for ischemic and 9.1 for hemorrhagic stroke. Other vascular conditions at elevated risk were myocardial infarction and other heart diseases (OR 2.1), thromboembolic conditions (OR 3.2), hypertension (OR 8.6), pregnancy-hypertension and preeclampsia (OR 2.3) [91].

Banhidy et al. Conducted a similar study analyzing retrospectively data from the Hungarian Case-Control System of Congenital Abnormalities between 1980 and 1996 [92]. They collected data from 38,151 infants, 713 (1.9%) of them were born from mothers with a migraine diagnosis. The risk of congenital malformations was not

increased but migraine was associated with a 1.4-fold higher risk of preeclampsia [92]. Also Chen et al. Detected in a retrospective study on 4911 Taiwanese women with migraine an elevated risk for preeclampsia (OR 1.3), when compared to 24,555 women without migraine. Moreover, they detected an elevated risk for preterm birth (OR 1.24) and low birth weight (OR 1.2) [93].

Comparable results regarding elevated risk for preeclampsia were collected by Simbar et al. In a retrospective study on 180 Iranian pregnant women; those with a history of migraine had a 2.7-fold higher risk for developing preeclampsia [94].

In one prospective study, Facchinetti et al. Examined the data of 702 pregnant women who were normotensive before pregnancy; the 38.5% of them reporting migraine headache had a 2.8-fold higher risk of developing hypertensive disorders during pregnancy [95]. This risk was particularly elevated for women with active migraine during pregnancy and remained significant even after adjusting for other common risk factors for hypertension such as age, smoking and positive family history. Women with migraine were also at a 1.9-fold higher risk for giving birth to low birth weight infants [95].

Similar results were reported in a more recent, smaller study by Grossman et al. [96]. They analyzed retrospectively the data of 86 pregnant women with migraine, who gave birth between 2009 and 2014. Their cohort consisted mostly of African-American and Hispanic women. In comparison with national averages, patients experiencing severe migraine attacks during pregnancy had a higher rate of complications during pregnancy and delivery, including preeclampsia (21.3% vs. 4%), preterm delivery (28.0% vs. 11.4%) and low birth weight (18.7% vs. 8%) [96]. Moreover, if migraine patients develop preeclampsia, they have also an increased risk for cerebral palsy and perinatal death [97].

The relationship between migraine and other vascular conditions remains unclear and is most probable related to overlapping pathophysiological mechanisms [21]. In the mentioned studies, the authors discuss possible common etiological backgrounds, including platelet hyperaggregation, decreased prostacyclin production, altered vasoreactivity and endothelial dysfunction [3, 98]. Supposedly, women with migraine have poor vascular compensation mechanisms in stress situations like pregnancy, leading in return to a higher incidence of vascular complications [91].

The risk of developing hypertensive disorders appears particularly high if other comorbidities are present. Czerwinski et al. Detected a 2.5-fold higher risk of developing pregnancy-induced hypertension in patients with migraine and additionally asthma [99]. Also comorbid mood-disorders can increase the risk of preterm birth and hypertensive disorders in pregnant migraineurs [100].

Furthermore, migraine is associated with a higher risk of nausea and hyperemesis gravidarum [92, 101]. Pregnant migraineurs complain significantly more often about short sleep duration, excessive daytime sleepiness, vital exhaustion and elevated perceived stress [102, 103].

Patients with migraine also have an elevated risk for depression during pregnancy and increased rates of anxiety and stress, especially in cases of migraine with aura [100, 103]. Some authors suggest that migraine and depression may share a common pathophysiology with dysfunction in the serotonergic and dopaminergic system [100].

Pregnancy complications in patients with other headache conditions

Only few studies included pregnant patients with other primary headache conditions than migraine. Maggioni et al. Conducted a retrospective study on 430 women after delivery: 126 (29.3%) suffered from primary headache disorders, among them 81 had MO, 12 MA and 22 TTH [5]. They detected no differences in APGAR scores (a method to quickly summarize the health of newborn children) and malformations between women with and without primary headaches, regardless of the headache subtype [5].

Sanchez et al. Observed that history of headache correlated significantly with placental abruption, i.e. The separation of the placenta from uterus before delivery [104]. The odds ratio for MA was 1.59, for MO was 2.11 and for TTH was 1.61 [104].

Finally, Marozio et al. Conducted a prospective study on 376 pregnant women with headache compared to 326 pregnant women without headache [105]. Among women with headache, 264 had migraine with or without aura and 103 a TTH. Preterm deliveries occurred significantly more often within the headache group and headache subtypes did not differ regarding pregnancy complications [105].

In conclusion, migraine is a risk factor for pregnancy complications, particularly vascular events [39, 97]. The risk of gestational hypertension and preeclampsia is increased in pregnant migraineurs and active migraine during pregnancy is associated with increased risk for stroke, cardiac diseases and thromboembolic events [39]. Therefore, migraineurs should be considered at higher risk for complications during pregnancy and monitored closely [39].

Data regarding other primary headache conditions are scarce. Although some authors suggested a higher risk for pregnancy complications in all headache patients regardless of the subtype, further research is needed to validate these results and examine possible common etiological factors [105].

Diagnostics of headache in pregnancy

Headache during pregnancy can be both primary and secondary, and in the last case can be a symptom of a life-threatening condition. During pregnancy, migraine and TTH are most common, however, there may occur conditions that resemble primary headaches but are symptoms of disorders first appearing during pregnancy. Early diagnostics of the disease manifested by headache is important for mother and fetus life.

For a differential diagnostics of headaches is important to collect the anamnesis: it is necessary to investigate family aptitude to headache, the age of its debut, whether it is a new or emerging condition; it is also important get a detailed description of its episode and its accompanying symptoms. The presence of headache before pregnancy is an important predictor of its development during or after pregnancy. It is also important to find out possible associated diseases that could trigger or worsen the course of headache. In addition, it is mandatory to consider administered medications. If there is a suspicion of the symptomatic character of the headache, it is necessary to carry out a neuroimaging, lumbar puncture and other methods [38].

Primary headaches during pregnancy

When MA occurs for the first time during pregnancy, it is necessary to conduct brain MRI to prevent ischemic stroke. Generally, migraine does not affect the outcome of pregnancy, but it is more likely to experience premature birth and preeclampsia [25, 106].

In addition to migraine during pregnancy, TTH is also quite common. The nature of pain, its localization, duration, as well as the conditions under which pain occurs, worsens and weakens play role in its diagnostics. In case of prolonged headache not improved by analgesics, it is advisable to perform ophthalmoscopy and brain MRI to exclude volume formations and intracranial hypertension.

Cluster headache is a relatively rare type of headache. Its extensiveness is approximately 0.06% of the population, with a total ratio of men to women of approximately 2.5:1 [57]. To exclude the secondary nature of the headache, it is also advisable to perform brain MRI.

Secondary headaches during pregnancy

It is especially important to identify “red flags” suggesting that headache is a symptom of a serious disease (Table 2). In these cases, electroencephalography, ophthalmoscopy, ultrasound of the vessels of the head and neck, brain MRI and MR angiography may be needed [38]. In some cases, it is possible to perform multi-slice computed tomography (MSCT). The risk for the fetus in this case is minimal and the contraindication is the mother allergy to the contrast agent [107].

Clinically, the most significant causes of the secondary headache in pregnant women are: stroke, subarachnoid hemorrhage, cerebral venous thrombosis, arterial dissection, pituitary tumor, choriocarcinoma, eclampsia, preeclampsia, posterior reversible encephalopathy syndrome, idiopathic intracranial hypertension, and reversible cerebral vasoconstriction syndrome.

Stroke (acute cerebrovascular accident)

To identify the etiology and make a diagnosis of ACA in pregnant women and puerperas, one or more of the following methods can be required: MRI and angiography, computed tomography (CT), MSCT, ophthalmoscopy electrocardiography and echocardiography, daily monitoring of arterial pressure and electrocardiograms, ultrasound examination of extra- and intracranial vessels with duplex scanning, and cerebral angiography [108].

Subarachnoid hemorrhage

Subarachnoid hemorrhage is caused by rupture of aneurysm or vascular malformations (arteriovenous malformation, cavernous or venous hemangioma). Intracerebral hemorrhages in pregnant women are rare. The risk of SAH is especially high in the first few days after birth. Diagnosis is confirmed by non-contrast-enhanced CT scan, which has a sensitivity of 98% in the first 12 h after onset [42]. If CT results are non-diagnostic, a lumbar puncture is essential. MRI is not indicated as an initial diagnostic test for SAH but may be useful when the CT is normal and the CSF abnormal [42]. Also, cerebral angiography can be performed, which allows determining the number of aneurysms and arteriovenous malformations, as well as their localization [108].

Cerebral venous thrombosis

CVT is a serious secondary headache disorder that can occur with pregnancy, usually during the 3rd trimester and postpartum period. Given the absence of specific characteristics, any recent persisting headache should raise suspicion, particularly in the presence of risk factors for CVT, such as hypertension, prothrombotic conditions, cesarean delivery, advanced maternal age, infections, and excessive vomiting. The rate of death with CVT is 2–10%, but less when associated with pregnancy [109]. Diagnosis is based on neuroimaging: MRI plus MRA, or CT scan plus CT angiography, and intra-arterial angiography in doubtful cases.

Arterial dissection

Headache associated to arterial dissections has no constant specific pattern and it can sometimes be very misleading, mimicking other headaches such as migraine, CH or primary thunderclap headache [42]. A painful Horner’s syndrome, painful tinnitus of sudden onset or painful xiith nerve palsy are highly suggestive of carotid artery dissection. Cervical artery dissection may be associated with

intracranial artery dissection, which is a potential cause of or intracranial haemorrhages (subarachnoid or intracerebral).

Headache attributed to cervical arterial dissection usually precedes the onset of ischaemic signs, and therefore requires early diagnosis and treatment. Diagnosis is based on cervical MRI, Duplex scanning, MRA and/or CTA and, in doubtful cases, conventional angiography [42]. Several of these investigations are usually needed as any of them can be normal.

Pituitary tumor

Pituitary tumors account for 10% to 22% of all neoplasms of the brain. One of the most common pituitary tumors is prolactinoma. In most cases, the pathology proceeds without any apparent symptoms. Visual disturbance and headaches occur only when the size of the tumor increases and is more than one centimeter. During pregnancy it is occurs rarely.

Microadenoma and pregnancy are poorly compatible with each other. In many cases, spontaneous abortion occurs in the first trimester. The most severe complication of the increase in size of a pituitary adenoma is apoplexy, resulting from hemorrhage or infarction of the tumor, which is usually accompanied by acute headache, visual impairment and pituitary dysfunction [110].

A pregnant woman with prolactinoma must be examined every 3 months and it is necessary to find out the presence of symptoms of tumor growth: headache, visual field disturbances, and abnormalities at the ophthalmoscopy [111]. MRI is performed only with the appearance of clinical symptoms indicating a tumor growth [112].

Choriocarcinoma

In Europe and North America, choriocarcinoma affects approximately 1 in 40,000 pregnancies [113]. A delay in diagnosis may lead to metastatic organ damage. When metastasizing in the central nervous system, there is headache, intense dizziness, darkening in the eyes, or other symptoms of volume formation in the brain. For diagnosis, brain MRI or CT scan can be sufficient and, if they result negative, a lumbar puncture can be performed. The determination of the concentration of chorionic gonadotropin (HCG) in the cerebrospinal fluid (CSF) and blood allows detecting initial metastases. HCG poorly penetrates the blood-brain barrier. A ratio of HCG concentration in the blood and in CSF less than 40:1 indicates the involvement of the CNS [114].

Headache associated with preeclampsia and eclampsia

Headaches are noted in 2/3 of all patients with preeclampsia or eclampsia [115, 116]. Preeclampsia is a preconvulsive condition characterized by a significant rise in blood pressure, a high protein concentration in the urine, and significant edemas. It occurs after the 20th week of pregnancy or in the postpartum period. Eclampsia is a convulsive seizure, which is preceded by a headache and a flash of light feeling. This state is either allowed or goes into a coma. Risk factors for the development of preeclampsia and eclampsia are overweight, hypertension, age over 40, diabetes, kidney disease, and multiple pregnancies. The occurring of preeclampsia increases the risk of hemorrhagic stroke developing during pregnancy and childbirth [117]. In addition, it is important to know that eclampsia is the most common cause of death of pregnant women [87, 118]. In women with eclampsia, seizures are preceded by headache similar to migraine, with pulsating character, different localization, accompanied by nausea or vomiting, photophobia and phonophobia [92]. The delayed postpartum eclampsia may occur within 1 week after childbirth, and its most common symptom is headache [119]. Each pregnant woman after 20 weeks of pregnancy suffering from a difficult-to-maintain headache should be examined for preeclampsia [120–124]. Diagnostic criteria for headache associated with preeclampsia and eclampsia are presented in the ICHD-3beta [42].

Posterior reversible encephalopathy syndrome

The clinical symptoms are usually non-specific and the differential diagnosis of PRES in pregnancy and puerperium may be challenging. The presentation can be mistaken for other conditions such as eclampsia, ischaemic and haemorrhagic stroke, CVT, RCVS, cerebral artery dissection, metabolic and demyelinating disorders, vasculitis and encephalitis [125]. CT imaging in PRES show lesions in only about 50% [126]. MRI represents the gold standard for this condition and leads to the correct diagnosis in most cases and may, therefore, forestall further investigations. Typical findings are bilateral and symmetrical white matter vasogenic oedema in the parieto-occipital regions; however, lesions can occur in both white and grey matter and can involve the frontal and temporal lobes, basal ganglia, brain stem and cerebellum [127].

Primary and secondary intracranial hypertension

The symptoms of idiopathic intracranial hypertension (IIH) are daily progressive non-pulsating headaches, which increase with the change in the body position and also with the Valsalva probe, with a transient feeling of darkening in the eyes and pulsating noise in the ears [121, 128, 129]. Most often IIH occurs in women of childbearing who are overweight. For the diagnosis is necessary to determine the absence of the brain substance defects and signs of thrombosis of the brain sinuses, therefore it is necessary to carry out brain MRI and MR angiography. In addition, it is necessary to define the absence of high pressure of CSF and changes in its composition. An important diagnostic sign is edema of the optic nerve disk

and progressive diplopia, which in the absence of adequate therapy, can be irreversible [121]. However, in one out ten cases otpic disk edema may be absent in IIH, since it takes weeks or months to develop [130].

The causes of secondary intracranial hypertension (SIH) may be different, including volume intracranial formations. More than the half of cases depends on venous sinuses thrombosis. The most frequent variant are thrombosis of cortical veins, causing headaches together with focal epileptic attacks, and thrombosis of the veins of the dura mater, resulting in a series of headaches, focal epileptic seizures and focal neurological deficiency. Cerebral vein thrombosis can occur during any gestation age, but more often in the postpartum period. MRI and MSCT venography are the most informative methods for detecting thrombosis of intracranial veins and sinuses [131].

Reversible cerebral vasoconstriction syndrome

Reversible cerebral vasoconstriction syndrome was considered a very rare disease in pregnant women, but over the time this condition became diagnosed more often, as postpartum angiography became possible to conduct [123]. The main symptom is "thunder-like headache" at the beginning of the disease with angiographic signs of vasoconstriction. The principal risk factor is a high concentration of vasoconstrictor substances in the body of a pregnant woman. This syndrome can also develop in the postpartum period due to the use of ergometrine maleate in postpartum hemorrhage [124]. The diagnostic criteria for headaches associated with reversible cerebral vasoconstriction syndrome are presented in ICHD-3beta [42].

Postpartum headache

In the postpartum period, the frequency of headache increases, mostly depending on the return of migraine, but also as a result of epidural anesthesia [120]. Headache that appeared after epidural anesthesia is quite typical. It is caused by a decrease in CSF pressure, occurs unexpectedly 1 to 7 days after puncture and has a positional character. Differential diagnosis of secondary headache in the postpartum period is carried out for postpartum eclampsia and subdural hematoma [121], angiopathy [132, 133], meningitis, cerebral thrombosis of veins and sinuses [120, 134], stroke, pituitary tumor, and chorioocarcinoma.

Conclusions

Headache is a common complaint in the general population, particularly in females. Therefore, it is not surprising that it is a frequent presentation in pregnant women. Primary headaches, such as migraine and tension headache, account for most headaches in pregnancy. Most women notice their headache either go away or greatly improve in the second and third trimesters of pregnancy, possibly due to a reduction in reproductive hormonal fluctuation. However, around 10% experience a worsening of symptoms and after delivery, most women quickly return to their pre-pregnancy migraine pattern.

Pregnancy creates alterations in maternal physiology that increase the risk of several dangerous secondary headache disorders, especially those associated with vascular endothelial dysfunction and hypertensive disorders of pregnancy. It is fundamental to consider secondary causes in the differential diagnosis of headache, which may require urgent investigation. Pre-eclampsia, eclampsia, CVT, certain types of ischemic and hemorrhagic stroke, SAH, pituitary apoplexy, RCVS, PRES, and thunderclap headache show an overlapping clinical presentations and need to be treated emergently. One or more between electroencephalography, ultrasound of the vessels of the head and neck, brain MRI and MR angiography with contrast, brain CT, ophthalmoscopy and lumbar puncture will distinguish primary and secondary headaches.

Pregnancy and lactation can complicate treatment options for women with migraine because of the risk of certain medications to the fetus and because medications are passed on in a mother's milk to varying degrees.

Paracetamol use in pregnancy is safe and ibuprofen can be prescribed for short-term use in the first and second trimesters. There are increasing safety data on triptans to treat migraine in pregnancy and, if other treatments have failed, sumatriptan may be used to treat acute migraine attacks also while nursing.

Options in prescription preventive medications are limited and it may be best to consider the safest interventions, which are lifestyle changes and behavioural treatment for stress management. When preventive pharmaceutical treatment is needed for migraine metoprolol and propranolol are the first choice followed by amitriptyline. Little data are available for Botulinum toxin type A use.

Acknowledgments

This manuscript is a product of the program School of Advanced Science promoted by the European Headache Federation (EHF-SAS).

Authors' contributions

All Authors on behalf of European Headache Federation contributed equally to the conception, design, drafting and critical revisions of the manuscript. All authors read and approved the final manuscript. NA, DZ, ITA, KS, OR, RB, TA are Junior Fellows of EHF-SAS and MDD and RU are Senior Fellows of EHF-SAS.

Competing interests

All the authors declared no competing interests related to the contents of this review. Furthermore, all authors declare that they have received no direct or indirect payment in preparation of this manuscript.

Publisher's Note

Author details
[1]Department of Clinical and Molecular Medicine, Regional Referral Headache Centre, Sapienza University of Rome, Sant'Andrea Hospital, 00189 Rome, Italy. [2]Department of Neurology, Ghent University Hospital, 9000 Ghent, Belgium. [3]Institute of Professional Education, Chair of Neurology. I.M. Sechenov First Moscow State Medical University, Moscow, Russia. [4]Danish Headache Center and Department of Neurology, Rigshospitalet Glostrup, -2600 Glostrup, DK, Denmark. [5]Department of Neurology, University of L'Aquila, 67100 L'Aquila, Italy. [6]Department of Neurology, Charité Universitätsmedizin Berlin, 10117 Berlin, Germany. [7]Department of Neurosciences, Headache Centre, University of Padua, 35128 Padua, Italy. [8]Neurology Department, Aeginition Hospital, National and Kapodistrian University of Athens, 11528 Athens, Greece.

Received: 1 September 2017 Accepted: 11 October 2017
Published online: 19 October 2017

References

1. The Lancet, at http://www.thelancet.com/gbd. Accessed 29 Oct 2016
2. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators (2016) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the global burden of disease study 2015. Lancet 8;388(10053):1545–1602
3. Menon R, Bushnell CD (2008) Headache and pregnancy. Neurologist 14(2): 108–119
4. Dixit A, Bhardwaj M, Sharma B (2012) Headache in pregnancy: a nuisance or a new sense? Obstet Gynecol Int 2012:697697
5. Maggioni F, Alessi C, Maggino T, Zanchin G (1997) Headache during pregnancy. Cephalalgia 17(7):765–769
6. Callaghan N (1968) The migraine syndrome in pregnancy. Neurology 18(2): 197–199
7. Somerville BW (1972) A study of migraine in pregnancy. Neurology 22(8):824–828
8. Granella F, Sances G, Zanferrari C, Costa A, Martignoni E, Manzoni GC (1993) Migraine without aura and reproductive life events: a clinical epidemiological study in 1300 women. Headache 33(7):385–389
9. Scharff L, Marcus DA, Turk DC (1997) Headache during pregnancy and in the postpartum: a prospective study. Headache 37(4):203–210
10. Marcus DA, Scharff L, Turk D (1999) Longitudinal prospective study of headache during pregnancy and postpartum. Headache 39(9):625–632
11. Granella F, Sances G, Pucci E, Nappi RE, Ghiotto N, Nappi G (2000) Migraine with aura and reproductive life events: a case control study. Cephalalgia 20(8):701–707
12. Mattsson P (2003) Hormonal factors in migraine: a population-based study of women aged 40 to 74 years. Headache 43(1):27–35
13. Sances G, Granella F, Nappi RE, Fignon A, Ghiotto N, Polatti F, Nappi G (2003) Course of migraine during pregnancy and postpartum: a prospective study. Cephalalgia 23(3):197–205
14. Kelman L (2004) Women's issues of migraine in tertiary care. Headache 44(1):2–7
15. Ertresvåg JM, Zwart JA, Helde G, Johnsen HJ, Bovim G (2005) Headache and transient focal neurological symptoms during pregnancy, a prospective cohort. Acta Neurol Scand 111(4):233–237
16. Melhado EM, Maciel JA Jr, Guerreiro CA (2007) Headache during gestation: evaluation of 1101 women. Can J Neurol Sci 34(2):187–192
17. Kvisvik EV, Stovner LJ, Helde G, Bovim G, Linde M (2011) Headache and migraine during pregnancy and puerperium: the MIGRA-study. J Headache Pain 12(4):443–451
18. macgregor EA (2014) Migraine in pregnancy and lactation. Neurol Sci 35(Suppl 1):61–64
19. Aegidius K, Zwart JA, Hagen K, Stovner L (2009) The effect of pregnancy and parity on headache prevalence: the head-HUNT study. Headache 49(6): 851–859
20. Aubé M (1999) Migraine in pregnancy. Neurology 53(4 Suppl 1):S26–S28
21. Contag SA, Mertz HL, Bushnell CD (2009) Migraine during pregnancy: is it more than a headache? Nat Rev Neurol 5(8):449–456
22. Torelli P, Allais G, Manzoni GC (2010) Clinical review of headache in pregnancy. Neurol Sci 31(Suppl 1):S55–S58
23. Nappi RE, Albani F, Sances G, Terreno E, Brambilla E, Polatti F (2011) Headaches during pregnancy. Curr Pain Headache Rep 15(4):289–294
24. Wright GD, Patel MK (1986) Focal migraine and pregnancy. Br Med J (Clin Res Ed) 293(6561):1557–1558
25. Goadsby PJ, Goldberg J, Silberstein SD (2008) Migraine in pregnancy. BMJ 336(7659):1502–1504
26. Bending JJ (1982) Recurrent bilateral reversible migrainous hemiparesis during pregnancy. Can Med Assoc J 127(6):508–509
27. Barbour PJ, Castaldo JE, Shoemaker EI (2001) Hemiplegic migraine during pregnancy: unusual magnetic resonance appearance with SPECT scan correlation. Headache 41(3):310–316
28. Turner DP, Smitherman TA, Eisenach JC, Penzien DB, Houle TT (2012) Predictors of headache before, during, and after pregnancy: a cohort study. Headache 52(3):348–362
29. Amir BY, Yaacov B, Guy B, Gad P, Itzhak W, Gal I (2005) Headaches in women undergoing in vitro fertilization and embryo-transfer treatment. Headache 45(3):215–219
30. Pearce CF, Hansen WF (2012) Headache and neurological disease in pregnancy. Clin Obstet Gynecol 55(3):810–828
31. van Vliet JA, Favier I, Helmerhorst FM, Haan J, Ferrari MD (2006) Cluster headache in women: relation with menstruation, use of oral contraceptives, pregnancy, and menopause. J Neurol Neurosurg Psychiatry 77(5):690–692
32. Robbins MS, Farmakidis C, Dayal AK, Lipton RB (2015) Acute headache diagnosis in pregnant women: a hospital-based study. Neurology 85(12): 1024–1030
33. Ramchandren S, Cross BJ, Liebeskind DS (2007) Emergent headaches during pregnancy: correlation between neurologic examination and neuroimaging. AJNR Am J Neuroradiol 28(6):1085–1087
34. Wall M (2017) Update on Idiopathic Intracranial Hypertension. Neurol Clin 35(1):45–57.
35. Hashmi M (2014) Low-pressure headache presenting in early pregnancy with dramatic response to glucocorticoids: a case report. J Med Case Rep 8:115
36. David PS, Kling JM, Starling AJ (2014) Migraine in pregnancy and lactation. Curr Neurol Neurosci Rep 14(4):439
37. Wells RE, Turner DP, Lee M, Bishop L, Strauss L (2016) Managing migraine during pregnancy and lactation. Curr Neurol Neurosci Rep 16(4):40
38. Mitsikostas DD, Ashina M, Craven A, Diener HC, Goadsby PJ, Ferrari MD, Lampl C, Paemeleire K, Pascual J, Siva A, Olesen J, Osipova V, Martelletti P, EHF committee (2015) European headache federation consensus on technical investigation for primary headache disorders. J Headache Pain 17:5
39. Wabnitz A, Bushnell C (2015) Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature. Cephalalgia 35(2):132–139
40. Bousser MG, Ferro JM (2007) Cerebral venous thrombosis: an update. Lancet Neurol 6(2):162–170
41. Loder E (2007) Migraine in pregnancy. Semin Neurol 27(5):425–433
42. Headache Classification Committee of the International Headache Society (IHS) (2013) The international classification of headache disorders, 3rd edition (β version). Cephalalgia 33(9):629–808
43. Verdelho A, Ferro JM, Melo T, Canhão P, Falcão F (2008) Headache in acute stroke. A prospective study in the first 8 days. Cephalalgia 28(4):346–354
44. Schwedt TJ, Dodick DW (2006) Thunderclap stroke: embolic cerebellar infarcts presenting as thunderclap headache. Headache 46(3):520–522
45. Linn FH, Rinkel GJ, Algra A, van Gijn J (1998) Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache. J Neurol Neurosurg Psychiatry 65(5):791–793
46. Shanmugalingam R, Reza Pour N, Chuah SC, Vo TM, Beran R, Hennessy A, Makris A (2016) Vertebral artery dissection in hypertensive disorders of pregnancy: a case series and literature review. BMC Pregnancy Childbirth 16(1):164
47. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB (2007) Narrative review: reversible cerebral vasoconstriction syndromes. Ann Intern Med 146(1):34–44
48. Brewer J, Owens MY, Wallace K, Reeves AA, Morris R, Khan M, Iamarca B, Martin JN Jr (2013) Posterior reversible encephalopathy syndrome in 46 of 47 patients with eclampsia. Am J Obstet Gynecol 208(6):468.e1–468.e6
49. Lee VH, Wijdicks EF, Manno EM, Rabinstein AA (2008) Clinical spectrum of reversible posterior leukoencephalopathy syndrome. Arch Neurol 65(2): 205–210
50. Schoen JC, Campbell RL, Sadosty AT (2015) Headache in pregnancy: an approach to emergency department evaluation and management. West J Emerg Med 16(2):291–301
51. Grand'Maison S, Weber F, Bédard MJ, Mahone M, Godbout A (2015) Pituitary apoplexy in pregnancy: a case series and literature review. Obstet Med 8(4):177–183
52. Dodick DW, Wijdicks EF (1998) Pituitary apoplexy presenting as a thunderclap headache. Neurology 50(5):1510–1511

53. Marcus DA (2002) Pregnancy and chronic headache. Expert Opin Pharmacother 3(4):389–393
54. Fox AW, Chambers CD, Anderson PO, Diamond ML, Spierings EL (2002) Evidence-based assessment of pregnancy outcome after sumatriptan exposure. Headache 42:8–15
55. Bohio R, Brohi ZP, Bohio F (2016) Utilization of over the counter medication among pregnant women; a cross-sectional study conducted at Isra University hospital, Hyderabad. J Pak Med Assoc 66:68–71
56. Duong S, Bozzo P, Nordeng H, Einarson A (2010) Safety of triptans for migraine headaches during pregnancy and breastfeeding. Can Fam Physician 56(6):537–539
57. Calhoun AH, Peterlin BL (2010) Treatment of cluster headache in pregnancy and lactation. Curr Pain Headache Rep 14(2):164–173
58. Airola G, Allais G, Castagnoli Gabellari I, Rolando S, Mana O, Benedetto C (2010) Non-pharmacological management of migraine during pregnancy. Neurol Sci 31(Suppl 1):S63–S65
59. Bendtsen L, Birk S, Kasch H, Aegidius K, Sørensen PS, Thomsen LL, Poulsen L, Rasmussen MJ, Kruuse C, Jensen R Danish headache society (2012) reference programme: diagnosis and treatment of headache disorders and facial pain. Danish headache society, 2nd edition, 2012. J Headache Pain 13 Suppl 1:S1–29
60. Coluzzi F, Valensise H, Sacco M, Allegri M (2014) Chronic pain management in pregnancy and lactation. Minerva Anestesiol 80(2):211–224
61. Amundsen S, Nordeng H, Nezvalová-Henriksen K, Stovner LJ, Spigset O (2015) Pharmacological treatment of migraine during pregnancy and breastfeeding. Nat Rev Neurol 11(4):209–219
62. Tepper D (2015) Pregnancy and lactation–migraine management. Headache 55(4):607–608
63. Mitsikostas DD, Vikelis M, Viskos A (2008) Refractory chronic headache associated with obstructive sleep apnoea syndrome. Cephalalgia 28(2):139–143
64. Hutchinson S, Marmura MJ, Calhoun A, Lucas S, Silberstein S, Peterlin BL (2013) Use of common migraine treatments in breast-feeding women: a summary of recommendations. Headache 53(4):614–627
65. Becker WJ (2015) Acute Migraine Treatment. Continuum (Minneap Minn) 21(4 Headache):953–972
66. Fox AW, Diamond ML, Spierings ELH (2005) Migraine during pregnancy: options for therapy. CNS Drugs 19(6):465–481
67. Olesen C, Steffensen FH, Sorensen HT, Nielsen GL, Olsen J (2000) Pregnancy outcome following prescription for sumatriptan. Headache 40(1):20–24
68. Hilaire ML, Cross LB, Eichner SF (2004) Treatment of migraine headaches with sumatriptan in pregnancy. Ann Pharmacother 38(10):1726–1730
69. Ephross SA, Sinclair SM (2014) Final results from the 16-year sumatriptan, naratriptan, and treximet pregnancy registry. Headache 54(7):1158–1172
70. Williams SH, Kehr HA (2012) An update in the treatment of neurologic disorders during pregnancy–focus on migraines and seizures. J Pharm Pract 25(3):341–351
71. Källén B, Lygner PE (2001) Delivery outcome in women who used drugs for migraine during pregnancy with special reference to sumatriptan. Headache 41(4):351–356
72. Källén B, Nilsson E, Otterblad Olausson P (2011) Delivery outcome after maternal use of drugs for migraine: a register study in Sweden. Drug Saf 34(8):691–703
73. Nezvalová-Henriksen K, Spigset O, Nordeng H (2013) Triptan safety during pregnancy: a Norwegian population registry study. Eur J Epidemiol 28(9):759–769
74. Wood ME, Lapane K, Frazier JA, Ystrom E, Mick EO, Nordeng H (2016) 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 30(2):190–200
75. Nezvalová-Henriksen K, Spigset O, Nordeng HM (2012) 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 52(8):1319–1320
76. Marchenko A, Etwel F, Olutunfese O, Nickel C, Koren G, Nulman I (2015) Pregnancy outcome following prenatal exposure to Triptan medications: a meta-analysis. Headache 55:490–501
77. Soldin OP, Dahlin J, O'Mara DM (2008) Triptans in pregnancy. Ther Drug Monit 30(1):5–9
78. Kurth T, Hernandez-Diaz S (2010) Commentary: Triptan use during pregnancy: a safe choice? Headache 50(4):576–578
79. Jürgens TP, Schaefer C, May A (2009) Treatment of cluster headache in pregnancy and lactation. Cephalalgia 29(4):391–400
80. Vanderpluym J (2016) Cluster headache: special considerations for treatment of female patients of reproductive age and pediatric patients. Curr Neurol Neurosci Rep 16(1):5
81. Marcus DA (2008) Managing headache during pregnancy and lactation. Expert rev Neurotherapeutics 8(3):385–395
82. Cassina M, Di Gianantonio E, Toldo I, Battistella PA, Clementi M (2010) Migraine therapy during pregnancy and lactation. Expert Opin Drug Saf 9(6):937–948
83. The Medical Letter, Inc. (2013) Warning against use of valproate for migraine prevention during pregnancy. Issue 1418(55):45
84. Marmura MJ (2017) Safety of topiramate for treating migraines. Expert Opin Drug Saf 13(9):12141–12147
85. Pariente G, Leibson T, Shulman T, Adams-Webber T, Barzilay E, Nulman I (2017) Pregnancy outcomes following in utero exposure to lamotrigine: a systematic review and meta-analysis. CNS Drugs 31(6):439–450
86. Veroniki AA, Rios P, Cogo E, Straus SE, Y F, Kealey R, Reynen E, Soobiah C, Thavorn K, Hutton B, Hemmelgarn BR, Yazdi F, D'Souza J, macdonald H, Tricco AC (2017) Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. BMJ Open 7(7):e017248
87. Morgan JC, Iyer SS, Moser ET, Singer C, Sethi KD (2006) Botulinum toxin a during pregnancy: a survey of treating physicians. J Neurol Neurosurg Psychiatry 77(1):117–119
88. Cohen S, Trnovski S, Zada Y (2001) A new interest in an old remedy for headache and backache for our obstetric patients: a sphenopalatine ganglion block. Anaesthesia 56(6):606–607
89. Govindappagari S, Grossman TB, Dayal AK, Grosberg BM, Vollbracht S, Robbins MS (2014) Peripheral nerve blocks in the treatment of migraine in pregnancy. Obstet Gynecol 124(6):1169–1174
90. Allais G, Gabellari IC, Borgogno P, De Lorenzo C, Benedetto C (2010) The risks of women with migraine during pregnancy. Neurol Sci 31(Suppl 1):59–61
91. Bushnell CD, Jamison M, James AH (2009) Migraines during pregnancy linked to stroke and vascular diseases: US population based case-control study. BMJ 338:b664
92. Bánhidy F, Acs N, Horváth-Puhó E, Czeizel AE (2007) Pregnancy complications and delivery outcomes in pregnant women with severe migraine. Eur J Obstet Gynecol Reprod Biol 134(2):157–163
93. Chen HM, Chen SF, Chen YH, Lin HC (2010) Increased risk of adverse pregnancy outcomes for women with migraines: a nationwide population-based study. Cephalalgia 30(4):433–438
94. Simbar M, Karimian Z, Afrakhteh M, Akbarzadeh A, Kouchaki E (2010) Increased risk of pre-eclampsia (PE) among women with the history of migraine. Clin Exp Hypertens 32(3):159–165
95. Facchinetti F, Allais G, Nappi RE, D'Amico R, Marozio L, Bertozzi L, Ornati A, Benedetto C (2009) Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. Cephalalgia 29(3):286–292
96. Grossman TB, Robbins MS, Govindappagari S, Dayal AK (2017) Delivery outcomes of patients with acute migraine in pregnancy: a retrospective study. J head face Pain 57(4):605–611
97. Blair E, Nelson K (2010) Migraine and preterm birth. J Perinatol 31(10):434–439
98. Allais G, Castagnoli Gabellari I, Airola G, Schiapparelli P, Terzi MG, Mana O, Benedetto C (2007) Is migraine a risk factor in pregnancy? Neurol Sci 28(Suppl 2):184–187
99. Czerwinski S, Gollero J, Qiu C, Sorensen TK, Williams MA (2012) Migraine-asthma comorbidity and risk of hypertensive disorders of pregnancy. J Pregnancy 2012:22–24
100. Cripe SM, Sanchez S, Lam N, Sanchez E, Ojeda N, Tacuri S, Segura C, Williams MA (2010) Depressive symptoms and migraine comorbidity among pregnant Peruvian women. J Affect Disord 122:149–153
101. Pakalnis A (2016) Migraine and hormones. Semin Pediatr Neurol 23(1):92–94
102. Williams MA, Aurora SK, Frederick IO, Qiu C, Gelaye B, Cripe SM (2010) Sleep duration, vital exhaustion and perceived stress among pregnant migraineurs and non-migraineurs. BMC Pregnancy Childbirth 10:72
103. Qiu C, Frederick IO, Sorensen T, Aurora SK, Gelaye B, Enquobahrie DA, Williams MA (2015) Sleep distrubances among pregnant women with history of migraine: a cross-sectional study. Cephalalgia 35(12):1092–1102
104. Sanchez SE, Williams MA, Pacora PN, Ananth CV, Qiu C, Aurora SK, Sorensen TK (2010) Risk of placental abruption in relation to migraines and headaches. BMC Womens Health 10:30
105. Marozio L, Facchinetti F, Allais G, Nappi RE, Enrietti M, Neri I, Picardo E, Benedetto C (2012) Headache and adverse pregnancy outcomes: a prospective study. Eur J Obstet Gynecol 161(2):140–143

106. Adeney KL, Williams MA (2006) Migraine headaches and preeclampsia: an epidemiologic review. Headache 46(5):794–803
107. Semere LG, mcelrath TF, Klein AM (2013) Neuroimaging in pregnancy: a review of clinical indications and obstetric outcomes. J Matern Fetal Neonatal Med 26(14):1371–1379
108. Shainker SA, Edlow JA, O'Brien K (2015) Cerebrovascular emergencies in pregnancy. Best Pract Res Clin Obstet Gynaecol 29(5):721–731
109. Preter M, Tzourio C, Ameri A, Bousser MG (1996) Long-term prognosis in cerebral venous thrombosis. Follow-up of 77 patients. Stroke 27(2):243–246
110. Nawar RN, abdelmannan D, Selman WR, Arafah BM (2008) Pituitary tumor apoplexy: a review. J Intensive Care Med 23(2):75–90
111. Molitch ME (2010) Prolactinomas and pregnancy. Clin Endocrinol 73(2):147–148
112. Karaca Z, Tanriverdi F, Unluhizarci K, Kelestimur F (2010) Pregnancy and pituitary disorders. Eur J Endocrinol 162(3):453–475
113. Lurain JR (2010) Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am J Obstet Gynecol 203(6):531–539
114. Caldas RF, Oliveira P, Rodrigues C, Reis I, Scigliano H, Nogueira R, Araújo C, Ferreira S (2017) Intraplacental Choriocarcinoma: rare or underdiagnosed? Report of 2 cases diagnosed after an incomplete miscarriage and a preterm spontaneous vaginal delivery. Case Rep Med 2017:7892980
115. Shah AK, Rajamani K, Whitty JE (2008) Eclampsia: A neurological perspective. J Neurol Sci 271(1–2):158–167
116. Cooray SD, Edmonds SM, Tong S, Samarasekera SP, Whitehead CL (2011) Characterization of symptoms immediately preceding eclampsia. Obstet Gynecol 118(5):995–999
117. Dangel AR, Atlas RO, Matsuo K (2009) Headaches in pre-eclampsia: a clinical dilemma in diagnosing intracranial hemorrhage. Eur J Obstet Gynecol Reprod Biol 146(2):232–233
118. Williams MA, Peterlin BL, Gelaye B, Enquobahrie DA, Miller RS, Aurora SK (2011) Trimester-specific blood pressure levels and hypertensive disorders among pregnant migraineurs. Headache 51(10):1468–1482
119. Al-Safi Z, Imudia A, Filetti L, Hobson D, Bahado-Singh R, Awonuga A (2011) Delayed postpartum preeclampsia and eclampsia: demographics, clinical course, and complications. Obstet Gynecol 118(5):1102–1107
120. Barrett J, Alves E (2005) Postpartum cerebral venous sinus thrombosis after dural puncture and epidural blood patch. J Emerg Med 28(3):341–342
121. Martin SR, Foley MR (2005) Approach to the pregnant patient with headache. Clin Obstet Gynecol 48(1):2–11
122. Woitzik J, Barth M, Tuettenberg J (2006) Persistent postpartum headache from a chronic subdural hematoma after peridural anesthesia. Obstet Gynecol 108(3 Pt 2):808–809
123. Sattar A, Manousakis G, Jensen MB (2010) Systematic review of reversible cerebral vasoconstriction syndrome. Expert Rev Cardiovasc Ther 8(10):1417–1421
124. Ishibashi T, Ishibashi S, Uchida T, Nakazawa K, Makita K (2011) Reversible cerebral vasoconstriction syndrome with limb myoclonus following intravenous administration of methylergometrine. J Anesth 25(3):405–408
125. Cozzolino M, Bianchi C, Mariani G, Marchi L, Fambrini M, Mecacci F (2015) Therapy and differential diagnosis of posterior reversible encephalopathy syndrome (PRES) during pregnancy and postpartum. Arch Gynecol Obstet 292(6):1217–1223
126. Roth C, Hügens-Penzel M, Ferbert A (2010) Posterior reversible encephalopathy syndrome (PRES). A relevant disease in intensive care medicine Intensivmed 47:520–525
127. Fugate JE, Claassen DO, Cloft HJ, Kallmes DF, Kozak OS, Rabinstein AA (2010) Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. Mayo Clin Proc 85(5):427–432
128. Biousse V, Ameri A, Bousser MG (1999) Isolated intracranial hypertension as the only sign of cerebral venous thrombosis. Neurology 53(7):1537–1542
129. Gilmore B, Michael M (2011) Treatment of acute migraine headache. Am Fam Physician 83:271–280
130. Hayreh SS (2016) Pathogenesis of optic disc edema in raised intracranial pressure. Prog Retin Eye Res. Jan;50:108–144
131. Crawford SC, Digre KB, Palmer CA, Bell DA, Osborn AG (1995) Thrombosis of the deep venous drainage of the brain in adults. Analysis of seven cases with review of the literature. Arch Neurol 52(11):1101
132. Bakhru A, Atlas RO (2010) A case of postpartum cerebral angiitis and review of the literature. Arch Gynecol Obstet 283(3):663–668
133. Fugate JE, Ameriso SF, Ortiz G, Schottlaender LV, Wijdicks EF, Flemming KD, Rabinstein AA (2012) Variable presentations of postpartum Angiopathy. Stroke 43(3):670–676
134. Karci A, Boyaci F, Yaka E, Cakmur R, Men S, Elar Z (2005) Cerebral venous thrombosis initially considered as a complication of spinal-epidural anaesthesia. J Int Med Res 33(6):711–714

Nederlandse samenvatting

Hoofdpijn bij een zwangere patiënte brengt specifieke uitdagingen met zich mee. Vrouwen gekend met een primaire hoofdpijn ervaren vaak een verandering van het hoofdpijnpatroon tijdens de zwangerschap, waarbij doorgaans een positieve evolutie wordt beschreven in het tweede en derde trimester. Tien procent van de zwangere hoofdpijnpatiënten geven echter een deterioratie van de klachten aan. Bijkomend zijn er ook vrouwen die zich presenteren met een nieuwe hoofdpijn tijdens de zwangerschap. Er zijn bepaalde types hoofdpijn, voornamelijk secundaire hoofdpijn zoals bijvoorbeeld een reversibel cerebraal vasoconstrictiesyndroom of een cerebraal veneuze sinustrombose, die zich vaker voordoen tijdens de zwangerschap. Zowel bij diagnostiek als behandeling van hoofdpijn zijn er beperkingen tijdens zwangerschap en borstvoeding.

Deze systematische review bundelt recente en relevante data over hoofdpijn tijdens de zwangerschap en borstvoeding. De meest voorkomende fenotypes worden beschreven met extra aandacht voor alarmsymptomen en secundaire hoofdpijn. Hoewel de diagnostische mogelijkheden tijdens de zwangerschap beperkter zijn, is het belangrijk om hoofdpijn tijdens de zwangerschap grondig uit te werken. In de meerderheid van de gevallen blijkt het om een primaire hoofdpijn te gaan, maar er zijn enkele niet te missen levensbedreigende aandoeningen voor moeder en kind zoals een subarachnoïdale bloeding of pre-eclampsie met hoofdpijn als presenterend symptoom.

De behandeling van hoofdpijn tijdens de zwangerschap en borstvoeding is een bijkomende uitdaging. Enerzijds blijft de eerste keuze behandeling niet-medicamenteus, gezien het risico op teratogeniciteit. Hier spelen levenshygiënische maatregelen en trigger management een centrale rol, maar hebben ook relaxatietechnieken, fysieke activiteit en gedragstherapie een aandeel. Anderzijds blijkt dat een onderbehandelde hoofdpijn kan lijden tot slaapdeprivatie, stemmingsstoornissen en stress wat op zijn beurt een negatieve invloed kan hebben op moeder en kind. Bijgevolg is het te verdedigen om voor een medicamenteuze strategie te kiezen, wanneer een conservatief beleid faalt. Voor- en nadelen van dergelijke aanpak dienen steeds in overleg met de patiënte overwogen te worden. Een basisregel is om steeds naar de laagst effectieve dosis en de kortst mogelijke behandelingsduur te zoeken. De verschillende aanvals- en

onderhoudsbehandelingen en gekende mogelijke nevenwerkingen voor het kind worden systematisch besproken.

Delaruelle et al. The Journal of Headache and Pain (2018) 19:117
https://doi.org/10.1186/s10194-018-0922-7

The Journal of Headache and Pain

REVIEW ARTICLE Open Access

Male and female sex hormones in primary headaches

Zoë Delaruelle[1*], Tatiana A. Ivanova[2], Sabrina Khan[3], Andrea Negro[4], Raffaele Ornello[5], Bianca Raffaelli[6], Alberto Terrin[7], Dimos D. Mitsikostas[8], Uwe Reuter[9] and on behalf of the European Headache Federation School of Advanced Studies (EHF-SAS)

Abstract

Background: The three primary headaches, tension-type headache, migraine and cluster headache, occur in both genders, but all seem to have a sex-specific prevalence. These gender differences suggest that both male and female sex hormones could have an influence on the course of primary headaches. This review aims to summarise the most relevant and recent literature on this topic.

Methods: Two independent reviewers searched PUBMED in a systematic manner. Search strings were composed using the terms LH, FSH, progesteron*, estrogen*, DHEA*, prolactin, testosterone, androgen*, headach*, migrain*, "tension type" or cluster. A timeframe was set limiting the search to articles published in the last 20 years, after January 1st 1997.

Results: Migraine tends to follow a classic temporal pattern throughout a woman's life corresponding to the fluctuation of estrogen in the different reproductive stages. The estrogen withdrawal hypothesis forms the basis for most of the assumptions made on this behalf. The role of other hormones as well as the importance of sex hormones in other primary headaches is far less studied.

Conclusion: The available literature mainly covers the role of sex hormones in migraine in women. Detailed studies especially in the elderly of both sexes and in cluster headache and tension-type headache are warranted to fully elucidate the role of these hormones in all primary headaches.

Keywords: Primary headache, Migraine, Tension-type headache, Cluster headache, Sex hormones, Estrogen, Testosterone, Gender

Introduction

The primary headaches covered in this review are tension-type headache (TTH), migraine and cluster headache (CH). All three entities occur in both men and women, yet display a sex-specific prevalence. These gender differences suggest that both male and female sex hormones could have an influence on the course of primary headaches.

TTH has a female preponderance, and is 1.5 times more frequent in women than in men [1]. CH, on the other hand, appears to have a higher incidence in men, specifically during young adulthood and middle age. Later in life the prevalence of CH evens out between the sexes [2]. Within the group of primary headaches the role of sex hormones has been studied most profoundly in migraine. Prepubertal children have a 3-10% prevalence of migraine without any gender difference [3, 4]. With onset of puberty and its associated hormonal changes, migraine becomes 2–3 times more common in women than in men, suggesting that migraine is influenced by the fluctuating hormonal status through menarche, menstruation, pregnancy, menopause, as well as the use of oral contraceptives and hormonal replacement therapy (HRT) [1, 3, 5–8].

In contrast, the course of migraine throughout the lifespan of men appears relatively stable, further pointing to the unique role of female sex hormones in the migraine phenotype [1]. Here, we summarise relevant literature of the last 20 years covering the influence of female and male sex hormones on primary headaches.

* Correspondence: zoe.delaruelle@uzgent.be
[1]Department of Neurology, University Hospital Ghent, Corneel Heymanslaan 10, 9000 Ghent, Belgium
Full list of author information is available at the end of the article

Search strategy and selection criteria

Two independent reviewers conducted a search on PubMed, using their own search string, composed of terms like LH, FSH, Progesteron*, estrogen*, DHEA*, Prolactin, Testosterone, androgen*AND Headach* OR Migrain* OR "Tension type" OR Cluster. This general search was performed on December 7th, 2017. In light of the large amount of published work on the topic and considering the evolution of the diagnostic criteria over time, the first search was conducted respecting a timeframe of 20 years, covering articles published after January 1st 1997. The initial screening was performed based on eligibility of title and abstract. Exclusion criteria included non-availability of abstract, animal studies, and articles in any language other than English. Original studies, published in full, constitute the core of this review. Other quoted references include systematic reviews, case reports, meta-analysis, Cochrane reviews, letters, lectures and comments. Any relevant publications cited in the eligible articles were also included. Differences between reviewers were resolved by careful discussion.

Results

Women

Childhood and adolescence

Almost 60% of girls and 50% of boys suffer from headache at some time during childhood and adolescence, with the prevalence increasing significantly during adolescence in girls, whereas it remains stable for boys [9]. The incidence of migraine is similar in both sexes until the age of 9 (2.5% of girls and 2.4% of boys) and then diverges to the disadvantage of girls [6]. Teenagers who suffer from headache are at greater risk of having headache in adulthood [9].

It is known that during puberty, sexual steroid hormones affect neural circuits and cause permanent changes in important brain areas such as the hypothalamus and the insula [4]. Onset of migraine frequently occurs around the time of menarche, as cyclic hormonal changes begin. Early menarche appears to be a risk factor for the development of migraine [6, 10]. Notably, the first menstrual cycles are often anovulatory and in general ovulation occurs one or two years later. In the USA, the average age of menarche is 12.8 years, but this may vary geographically. Migraine with aura has an incidence peak between ages 12 to 13, while migraine without aura typically presents a few years later. Thus, migraine without aura may be associated with the establishment of a regular ovulatory menstrual cycle [7]. Headaches are reported in 53% of adolescent girls at the onset of menses. Pubertal development and age seem to modulate the effect of ovarian hormones on migraine. In fact, high urinary levels of pregnandiol glucuronide, a metabolite of progesterone, are associated with a higher migraine frequency in girls before menarche, but with a lower frequency after menarche [11]. Hershey et al. identified specific genomic patterns in girls suffering from menstrual migraine, suggesting a genetic predisposition for the development of this condition during adolescence [12].

TTH shows a similar, increasing trend in girls by the time of menarche. The incidence ratio between boys and girls changes from 1.3:1 during childhood to 1:1.2 after menarche [13].

It is noteworthy to mention, that pathological changes in sexual hormones can cause a secondary headache. For instance, hyperprolactinemia manifests in up to 45% of childhood cases with headache as a first symptom [14–16].

Adulthood

Migraine Women have a 3.25-fold higher risk of suffering from migraine than men [17]. A prevalence peak is reached in women between the ages of 35 and 45, with 25-30% of the general female population being affected, in comparison to only 8% of the general male population [18]. Female migraine patients also report a significant higher burden of disease and greater use of analgesic compared to men [6, 13].

In terms of deciphering the pathophysiological mechanism of the preponderance of migraine in women, neuroimaging studies have revealed sex-specific activation patterns, with an increased activation of the insula and precuneus in women. These regions are involved in pain, sensation and affective processing [19]. Sex hormones can cross the blood-brain barrier passively and are at least partially responsible for these sex differences [18]. Most available literature focuses on the effects of estrogen, while the role of progesterone has been less thoroughly investigated.

The relationship between estrogen and migraine is complex, involving modulation by genomic and non-genomic effects [20, 21]. Obese women appear to have more than a twofold risk of episodic and chronic migraine, probably due to the pathological estrogen production in adipose tissue [22, 23]. Substantial evidence points to the serotonergic system as a key player in migraine pathogenesis [7]. Estrogen modulates serotonergic neurotransmission, by increasing the expression of the tryptophan hydroxylase and decreasing the expression of the serotonin reuptake transporter [7, 24, 25]. Estrogen also activates the endogenous opioidergic system, which has an analgesic effect on persistent, inflammatory pain [26]. Furthermore, estrogen induces vascular changes by modulating vasodilation and suppressing vascular inflammatory responses [6, 27, 28].

The levels of calcitonin gene-related peptide (CGRP), a neuropeptide with a key role in migraine pathophysiology, are higher in women of reproductive age than in

men. Cyclic hormonal fluctuations influence CGRP release and consequently the trigeminovascular system [29]. While studies have reported a positive relationship between CGRP and estrogen levels, newer studies suggest an inverse relationship between the two [24].

Experimental studies suggest progesterone to play a protective role, by reducing nociception in the trigeminovascular system, inhibiting neurogenic edema, and histamine secretion from mast cells and decreasing prostaglandin production [7, 24, 30, 31].

Multiple studies have examined the association between polymorphisms in estrogen or progesterone receptor genes and migraine risk, with inconclusive findings [32–37]. In their meta-analysis, Schürks et al. and Li et al. concluded that exon 4 325C > G and exon 8 594G > A polymorphisms are risk factors for migraine, while the often examined PROGINS variant in the progesterone receptor gene did not seem to play a significant role in the Caucasian population [38, 39]. On the contrary, Joshi et al. found a protective role of the PROGINS polymorphism in an Indian population [40].

Prolactin could also play a modulatory role in migraine. Parashar et al. found higher prolactin levels in migraineurs compared to controls [41]. An association between high prolactin levels and migraine chronification has been proposed by Cavestro et al. [42], where Peres et al. detected decreased nocturnal prolactin peaks in chronic migraine patients [43].

There are a few reports suggesting that testosterone can play a role in migraine in women [44, 45]. In one case report, the 5α reductase inhibitor finasteride was administered to a young woman with migraine and led to an almost complete remission [45]. The mechanism of action of testosterone on migraine pathophysiology is still unknown, but may involve modulation of cerebral blood flow, serotonergic tone, and susceptibility to cortical spreading depression [44].

Menstrual migraine The probability of migraine to occur during the perimenstrual period is twice as high compared to any other moment of the menstrual cycle [46]. Almost half of female migraine patients report an association between headache and their menstrual cycle [17]. Depending on whether migraine occurs exclusively during the perimenstrual period or also at other times, the International Headache Society (IHS) distinguishes a pure menstrual migraine from a menstrually-related migraine (Table 1). Migraine associated with menstruation is mostly of the type without aura [21].

Pure menstrual migraine and menstrually-related migraine have an overall prevalence of respectively 1% and 7% in the general population [47]. Data from specialized headache clinics suggest that perimenstrual attacks are more severe, long-lasting and difficult to treat with abortive anti-migraine medication [48]. However, these results could not be confirmed in the general population [49]. Menstrual migraine appears to limit work and social activities more frequently than common migraine and is often associated with a dysphoric mood [17].

The "Estrogen withdrawal hypothesis", developed by Somerville and colleagues in 1972, postulates that attacks of menstrual migraine are triggered by the decrease in estrogen levels preceding menstruation [21]. A drop in estrogen may cause an increased sensitivity to prostaglandins and a release of neuropeptides such as CGRP, substance P and neurokinins which could result in neurogenic inflammation [17]. This physiological response provokes alterations in the microvasculature of the dura mater, changes in calcium and magnesium concentrations, and an imbalance in serotonin and dopamine concentrations [17, 21, 50]. Estrogen withdrawal might lead to an increased oxidative stress in the cells [51]. To confirm this hypothesis, intramuscular injections of estrogen were administered before menstruation and thereby postponing migraine attacks [52, 53]. On the contrary, progesterone injections only led to postpone menses, but not migraine [52, 54].

More recent studies confirm that an estrogen drop can trigger migraine, especially if this drop is preceded by a phase of high estrogen levels, as in the luteal phase of the menstrual cycle, and if the magnitude of the decrease is greater than 10 μg [55, 56]. Interestingly, women with migraine seem to have a faster drop in estrogen levels than non-migraineurs [57].

Welch et al. tried to explain estrogen effects on menstrual migraine with a "mismatch theory". Under normal circumstances, genomic effects of estrogen can counterbalance non-genomic mediated membrane excitability.

Table 1 IHS classification (ICHD-3) for pure menstrual and menstrually-related migraine

Pure menstrual migraine	Menstrually-related migraine
A. Attacks, in a menstruating woman, fulfilling criteria for migraine without aura	A. Attacks, in a menstruating woman, fulfilling criteria for migraine without aura
B. Attacks occur exclusively on day 1 ± 2 (i.e, days − 2 to + 3)[a] of menstruation[b] in at least two out of three menstrual cycles and at no other times of the cycle	B. Attacks occur on day 1 ± 2 (i.e, days − 2 to + 3)[a] of menstruation[b] in at least two out of three menstrual cycles and additionally at other times of the cycle

[a]The first day of menstruation is day 1 and the preceding day is day − 1; there is no day 0
[b]For the purposes of this classification, menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the case of combined oral contraceptives and cyclical hormone replacement therapy

In low estrogen states, this inhibiting genomic effect does not suffice, and migraine attacks occur more frequently [58, 59].

In one retrospective study with 85 female patients with menstrual migraine, 35.3% reported migraine headache onset by the end of menstruation, which is days after the estrogen drop. The authors hypothesize that this type of migraine headache is not related to hormonal changes but most probably to transient anemia due to blood loss [56].

Hormonal treatment of menstrual migraine, like perimenstrual application of estrogen gel or a transdermal estradiol patch, can lead to less frequent, shorter and less intensive attacks [46, 47, 52, 60]. Attacks may recur after discontinuation of hormonal treatment [17]. Following the estrogen withdrawal hypothesis, eliminating estrogen cycling appears to be a useful strategy for long-term prophylaxis of menstrual migraine. Therefore, continuous combined contraceptive therapy regimes, containing both estrogen and progesterone, can be considered. However, there is currently no evidence that hormonal therapy is more effective than non-hormonal pharmacological treatment strategies. Hormonal therapy is particularly recommended if other indications like acne or hirsutism exist. Contraindications should be ruled out [17, 53]. Alternatively, progesterone-only contraceptives can be considered. A significant reduction in migraine intensity and frequency is reported [17, 61–63]. As progesterone has no experimental effect on cortical spreading depression, progesterone-only contraception is hypothesized to be a safer choice for women with aura [62, 64], but no clinical evidence has confirmed this theory. The selective estrogen receptor modulator Tamoxifen might also be beneficial in women with menstrual migraine. However, its use is not generally recommended due to possible and in part serious side effects [65]. Some studies suggest that phytoestrogens like soy isoflavone, dong quai or black cohosh could have a beneficial effect on migraine [17]. Martin et al. examined the efficacy of the gonadotropin-releasing hormone antagonist goserelin as a prophylactic therapy. Goserelin alone did not affect migraine headache frequency. Some benefit was obtained when combined with 100 μg estradiol [66]. Glaser et al. demonstrated that continuous testosterone therapy through a subcutaneous implant for 3 months led to headache improvement in 92% of migraine patients [44].

Migraine with aura The female dominance is also seen in migraine with aura. In prevalence studies performed after 1988 it reaches a prevalence of 1.2-3.7% in men and 2.6-10.8% in women [67]. In contrast to menstrual migraine, migraine with aura occurs more frequently with high estrogen levels [68]. Estrogen seems to change cortical susceptibility and contributes to the development of cortical spreading depression. The amplitude of the spreading depression depends on the estrogen level [69]. The threshold for cortical excitability and subsequent cortical spreading depression is lowered through several genomic and non-genomic mechanisms, including upregulation of NMDA receptors, downregulation of GABA neurons and modulation of axonal plasticity [4, 69, 70].

Exogenous hormone-induced headache In the Western world, almost one third of women of reproductive age use oral contraception [55]. The IHS identifies two headache entities related to the use of hormonal contraceptives: exogenous hormone-induced headache and estrogen-withdrawal headache (Table 2).

Headache is one of the most common side effects of hormonal therapies [71]. For instance Tamoxifen, mentioned above as a possible treatment for menstrual migraine, can also cause headache. The onset of hormone-induced headache is typically within the first months of use [72]. Combined contraception remedies (oral pill, transdermal patch, vaginal ring) appear to be associated with both migraine and non-migraine headaches [73]. The effect in migraine patients is variable. One out of two female migraine patients report no change of the headache pattern, 15% experience an improvement, while 28% report worsening [74]. A negative effect occurs more often in migraine with aura [72]. Headaches most frequently occur in the “pill-free” week [53]. The neuronal nociceptive sensitivity is increased in this week and the probability of getting a headache is 20% higher [74, 75]. Higher age (> 35 years) and a positive family history for migraine are risk factors [76, 77].

Possible contraceptive strategies to reduce headache include extended-cycle combined hormonal contraception,

Table 2 IHS classification (ICHD-3) for exogenous hormone-induced headache and estrogen-withdrawal headache

Exogenous hormone-induced headache	Estrogen-withdrawal headache
A. Headache or migraine fulfilling criteria C and D	A. Headache or migraine fulfilling criteria C and D
B. Regular use of exogenous hormones	B. Daily use of exogenous estrogen for ≥3 weeks, which has been interrupted
C. Headache or migraine develops or markedly worsens within 3 months of commencing exogenous hormones	C. Headache or migraine develops within 5 days after last use of estrogen
D. Headache or migraine resolves or reverts to its previous pattern within 3 months after total discontinuation of exogenous hormones	D. Headache or migraine resolves within 3 days of its onset

progesterone-only contraception or new generation hormones like estradiol valerate/dienogest [17, 62, 78, 79]. Eliminating the pill-free week is associated with improvement of headache, pelvic pain and quality of life [55].

In progestin-only methods (oral pill, subdermal implant, depot-injection, levonorgestrel-releasing intrauterine system) headache is a common complaint at the beginning of therapy but classically improves after a few months. There is no known association between progestin-only methods and the worsening of migraine [74]. On the contrary, frequency and intensity of migraine can significantly improve with this type of contraception. Ten percent of patients discontinue treatment due to side effects, particularly spotting [80, 81].

Migraine with aura is associated with a twofold risk of major cardiovascular events, like ischemic stroke. This risk is directly proportional to aura frequency [55]. In the meta-analysis of Schürks et al. a relative stroke risk of 1.73 (95% CI 1.31-2.29) was found for any type of migraine. The relative risk of stroke in women suffering from migraine with aura is 2.08 (95% CI 1.3-3.31). The relative risk of cardiovascular deaths in women with migraine is 1.60 (95% CI 1.72-2.43) [82]. Older combined hormonal therapies with high dosed estrogen (50–150 μg) are associated with a 4.4-fold risk of stroke in migraine patients, in particular in migraine with aura and should not be used anymore. The modern low-estrogen contraceptives (< 25 μg) seem much safer [55, 56]. The 2017 consensus statement from the European Headache Federation and the European Society of Contraception and Reproductive Health recommends against the use of combined hormonal contraceptives in women with migraine with aura seeking hormonal contraception. They postulate a strong recommendation to prefer non-hormonal (condoms, copper-bearing intrauterine device, permanent methods) or progestogen-only alternatives. The same strategy is preferred in women with migraine without aura who have additional cardiovascular risk factors, like smoking, arterial hypertension, previous history of a trombo-embolic event. When there are no such risk factors, combined hormonal contraceptives are considered a possible contraceptive option with monitoring of migraine frequency and characteristics in women without aura. Other medical conditions like polycystic ovary syndrome or endometriosis can influence the risk/benefit profile and have an impact on the preferred type of contraception [83].

Tension-type headache The impact of hormones on TTH is less frequently studied. Like migraine, TTH occurs more often in women than in men and some studies have suggested an increase during hormonal changes such as menses or pregnancy. Menstruation can be an aggravating factor in 40-60% of patients [13]. There is no evidence that TTH is influenced by hormonal contraception [77].

Cluster headache The hypothalamus is thought to be involved in CH pathophysiology based on its periodic time locked occurrence. Sex hormones appear to modulate hypothalamic activity and could be effective as a treatment for therapy refractory CH [84]. Both male and female cluster patients show low testosterone levels and testosterone supplementation could have a positive effect on headache attacks [2]. In the first studies from the early 1990s, testosteron supplementation did not prove effective, but more recent data show a good response in a subgroup of cluster patients [84]. Clomifen is a selective estrogen modulator, primarily used for ovulatory stimulation in women. In men, it leads to an increase in luteinizing and follicle stimulating hormones (LH, FSH) and subsequently to higher testosterone levels. Furthermore, in animal model, it reduces prostaglandine production [85]. In a case-series of 7 patients with chronic cluster headache and 8 patients with episodic cluster headache, Clomifen led to pain freedom after 15 days on average [84].

Evidence of dysregulation of the hypothalamus-hypophysial axis in trigeminal autonomic cephalgias could be derived from a case with high nocturnal prolactin levels in a female patient suffering from short, unilateral, neuralgiform headache with conjunctival injection and tearing (SUNCT) [86].

Other headache types Pituitary diseases are often associated with secondary headaches. Especially in female patients with prolactinoma, migraine-like headaches or worsening of a known migraine are reported. Mainly mechanic aspects such as compression of pain sensitive structures play a role in the development of headache, but probably increased hormonal secretion has an impact as well [87]. Prolactin is involved in regulation of neuronal excitability and neurotransmission efficacy [88]. Headache is commonly localized on the same side of the tumor and gets better after treatment with dopamine agonists [89, 90].

Perimenopause

Perimenopause is a period of decrease in reproductive capability in middle-aged women. During this period the growth and development of ovarian follicles stops and the pattern of estrogen and progesterone production changes. Signs of perimenopause include irregular menses and periodic amenorrhea starting several years before menopause, also called the menopausal transition. The average age of onset is 40 to 55 years and the average duration is 4 years, but in some women perimenopause can last from several months up to 10 years [91].

The Stages of Reproductive Aging Workshop developed a classification for staging reproductive aging dividing a women's life into three stages based on the menstrual cycle: premenopausal (or reproductive), perimenopausal (or menopausal transition) and menopausal (or postmenopause) phase. There are two phases in the menopausal transition: the early phase, characterized by a variable cycle length (≥ 7 days), and a late amenorrhea phase. Postmenopause can also be divided into two stages. An early stage that lasts 5 to 8 years, characterized by amenorrhea length more than 1 year, low estrogen levels and high FSH level. The late stage is characterized by stable low levels of ovarian hormones [92].

Perimenopause is characterized by fluctuations in both estrogen and progesterone levels. Due to these constant rapid changes in concentrations of ovarian hormones 60-70% of perimenopausal women experience symptoms such as headaches, flushing, mood swings, depression, decreased libido and sleep disturbance [91]. The decrease of estrogen in the late luteal phase leads to low blood serum estrogen and progesterone levels and promotes prostaglandins release by the uterus influencing the menstrual cycle. This estrogen withdrawal becomes more frequent and longer and can have a secondary impact on headache patterns [46, 93].

Migraine Studies show that migraine prevalence in menopause is lower compared to the perimenopausal period. Menopausal transition seems to negatively impact migraine frequency [94, 95]. As perimenopause and menopause consist of several phases, each with a unique hormonal pattern, they all have a different effect on migraine. Another important factor is whether the menopause is naturally or artificially induced and whether HRT is used [92].

Fluctuation in the estrogen level is a known migraine trigger. The hormonal alterations during perimenopause can provoke migraine attacks in 50% of women with menstrual migraine and menstrual related migraine. Rather stable levels of estrogen are replaced by a more fluctuating pattern with periods of rapid decline in estrogen concentration, the so called estrogen withdrawal [95–97]. The amount of estrogen withdrawal episodes is correlated to headache attack frequency in women with menstrual migraine in "early" perimenopause. Likewise women can experience an increase in menstruation frequency and in some cases an increase in vaginal bleeding duration and severity [98]. This is related to an increase in uterine prostaglandins, which also influences central pain mechanisms and the trigeminovascular system provoking menstrual migraine attacks [99, 100]. Another potential mechanism that can increase menstrual migraine attack frequency is iron deficiency caused by menstrual bleeding [101]. Depression, chronic pain syndrome and sleep disturbance can be other symptoms related to perimenopause, which in turn can lead to a secondary increase in migraine [102].

Women suffering from the premenstrual syndrome were shown to experience more migraine attacks in late perimenopause. The attack frequency declines in the menopausal period. The premenstrual syndrome seems a predictor of migraine attack frequency increase for women entering menopause. These women are considered to have high sensitivity to hormonal fluctuations and liability to moderately severe climacteric symptoms, which in turn can have an impact on migraine [92].

Migraine and hormonal replacement therapy (HRT) HRT is used to ease climax symptoms during menopausal transition. It seems to have a significant influence on migraine course. Studies confirm the correlation between the use of HRT, both oral and topical, and migraine [103, 104]. Oral high dosed estrogen can provoke new onset migraine with aura or worsening of pre-existent migraine with aura. Nappi et al. concluded that migraine deteriorated in women using oral estradiol plus medroxyprogesterone acetate. The course of the disease did not change with a transdermal patch [105]. A few years later MacGregor et al. showed that transdermal patches with estrogen can be effective in decreasing migraine attack frequency in perimenopausal and postmenopausal women, supposedly more effectively than oral contraceptives [106]. Gels and patches based on estradiol seem preferable over oral variants as constant blood hormones levels are maintained stable. They should be taken continuously without omission to prevent rapid changes in estrogen blood levels, a known trigger for migraine [105, 107]. These fluctuations in estrogen concentration have a more significant impact on migraine than progesterone levels. Nand et al. studied three groups of patients treated with different doses of progesterone combined with estrogen and revealed that changes in progesterone levels have no influence on migraine course [92].

HRT containing low doses of natural estrogens are linked to an insignificant risk of thromboembolism, in contrast to the above mentioned combined oral contraception. Nevertheless HRT should be stopped immediately in case of a new onset migraine with aura, a clear increase in frequency or worsening of migraine with aura, transitory ischemic attack or other vascular pathology [108].

Migraine and surgical menopause Natural menopause seems to reduce migraine frequency, in contrast to surgically induced menopause [5]. Neri et al. studied a group of postmenopausal women [109]. Improvement of migraine was seen in two thirds of cases compared to

the premenopausal period. At the same time no reduction in days with TTH was observed. In women, who underwent ovariectomy the course of migraine worsened in the majority of women (67%). Thirtythree percent reported migraine improvement. In women with natural menopause 67% reported improvement in migraine course, in 24% of patients no change was observed and 9% reported worsening [109]. There is still a debate on possible migraine worsening in women who undergo procedures such as hysterectomy, dilation and curettage or cesarean section. Arumugam and Parthasarathy found a positive correlation between these procedures and the prevalence of migraine in women [110]. Oldenhave et al. compared a group of 986 hysterectomized women and 5636 women without hysterectomy with one or both ovaries preserved. The amount of days without migraine in the group without hysterectomy was less compared to the hysterectomy group. This data confirms the importance of presence or absence of the uterus on migraine frequency in menopausal women [92].

Tension-type headache The most common risk factors for TTH are considered to be stress, fatigue and sleep disturbance. During perimenopause these symptoms can exacerbate and trigger TTH. But TTH also seems to have a correlation with reproductive hormone levels [111]. In some women menstruation can trigger TTH and also pregnancy and menopause can influence the course of TTH [93, 111]. In retrospective evaluations 38% to 46% of women reported an increase of headache rate during menstruation [112, 113]. Arjona et al. even tried to identify "menstrual TTH" and "menstrual related TTH" based on ICHD-2 criteria for pure menstrual migraine and menstrually-related migraine. These terms were not included into the ICHD [114]. Women in the perimenopause reported their headaches to have new characteristics and prevalence of TTH seems rather high [115]. The prevalence of TTH in postmenopausal women is reported to be higher than in premenopausal women [116].

Cluster headache According to the literature the course of CH in women is biphasic. The first peak of onset is seen around the age of 20 and the second at age 50 to 60. The majority of female cluster patients experience their first attack during menopause [116, 117]. The role of estrogen in CH and the reason for CH onset in these women remain unclear. Estrogen receptors are seen in the trigeminal ganglion and in sensory neurons which makes them susceptible to rapid changes in estrogen level [118]. In menopause the reduced level of estrogen is assumed to provoke CH, while the higher estrogen level in the premenopausal phase can have a protective effect [119]. However, based on the available literature, there is no clear evidence on the relationship between CH and hormonal changes in women [120, 121].

In 2006 van Vliet et al. published a large retrospective study in which data from more than 200 women with CH were analyzed using questionnaires. Among women with CH 9% reported more intense CH attacks during menstruation, while frequency didn't change. Eighty-six percent of women were using lifelong oral contraceptives in this trial. Initiation of oral contraceptives was associated with an increase of days with headache in 12% of participants. In 4% of the cases headache frequency was reduced. Out of 111 pregnant women with episodic CH 26 (23%) women reported "expected" CH attacks not to occur. After childbirth 8 of them experienced CH attacks in the first month. Nineteen patients (17%) had attacks during pregnancy and 11 of them did not report any changes in attack frequency or intensity [120].

Elderly

In the elderly, headache is less frequent compared to younger patients. Headache disorders are mostly primary, but the relative frequency of secondary headache is higher in the elderly [122]. In a random population sample, the prevalence of headache in women and men aged 55 to 74 years is approximately 66% and 53%, respectively, compared to 92% and 74%, respectively, in their younger counterparts between the ages of 21 to 34 years. The prevalence further declines in patients aged over 75 to 55% for women and 22% in men [123]. In a population survey, the prevalence of frequent headache in elderly women was 20% and 10% in elderly men [124]. Another survey showed a 3-month prevalence of headache among patients aged more than 66 years of 40.6% in men and 49.7% in women [125]. In summary, all studies show that headache is more prevalent in women compared to men at all ages, even among the elderly. Hormonal factors take account for the sex-specific difference in headache prevalence. However, literature data about the relationship between headache and hormonal activity in elderly women are scarce. Only the relationship between migraine and estrogen has been extensively studied in older women, possibly because of the high prevalence of migraine and its sensitivity to hormonal fluctuations.

Up to 51.9% of elderly patients referred for specialist consultation report onset of headache after 65 years of age [126]. Some primary headache disorders, and mostly hypnic headache, have the tendency to start after the age of 50, in contrast to most primary headache disorders, which usually start at a younger age. However, migraine still accounts for 0.5% of all new-onset headache disorders after the age of 65 [127, 128]. The low estrogen level in elderly women may explain why onset of migraine in this age group is uncommon. Migraine with

onset at older age affects women and men equally, while in younger age groups women outnumber men [129].

Migraine As mentioned above, the "estrogen withdrawal hypothesis" attributes migraine episodes to the fluctuation of estrogen levels throughout women's reproductive events. After menopause, women's serum levels of estradiol drop. A lower frequency and severity of migraine episodes is expected because of the stable low serum levels of estrogen. Migraine prevalence declines after menopause compared to the fertile period. However, the prevalence of migraine after the menopause is still 10 to 29% across studies [5].

Interestingly, the decreased burden of migraine after the menopause is more evident in population-based studies when compared with those performed in headache clinics or menopause clinics [94, 109, 115, 130–134]. This can be explained by a possible selection bias towards more severe forms of migraine in clinic-based studies as compared to population-based studies [5]. Menopause has a different and variable effect on migraine with or without aura [8]. In a population-based study, the burden of migraine without aura decreased after menopause while that of the variant with aura remained stable [130]. In a headache clinic-based study migraine without aura remained unchanged or even worsened in the majority of patients possibly because of the above mentioned selection bias of clinic-based studies [135]. Collectively, these data suggest that migraine without aura improves more frequently after menopause compared to migraine with aura. This can be a possible consequence of migraine without aura being more sensitive to female sex hormones [5]. However, the available studies might have failed to show any change in the frequency of migraine with aura after the menopause because of low statistical power [136]. When migraine with aura does not subside with age, characteristics may change, with increasing occurrence of aura without headache. These auras constitute a difficult differential diagnosis with transient ischemic attacks [137, 138]. An aura is generated by cortical spreading depression while migraine pain has been linked to the neurovascular system. Elderly subjects may exhibit an intact cortical spreading depression phenomenon, while the propensity to neurovascular inflammation declines [139]. It is likely that those changes can be a consequence of the postmenopausal estrogen drop. However, to the best of our knowledge, this has not been proven yet.

Together with female sex hormones, male sex hormones might have an influence on the course of headache disorders among elderly women. Only one case-control study assessed the levels of androstenedione and testosterone in the serum of postmenopausal women with and without migraine and found no differences in the levels of these hormones when comparing women with and without migraine [140].

In conclusion, the postmenopausal drop of estrogen might be beneficial for elderly women with migraine. However, the proportion of women experiencing migraine in menopause is still relevant.

Tension-type headache The effect of menopause on TTH is less clear than the corresponding effect on migraine. One population-based study addressing the topic found that the frequency of TTH decreased less than that of migraine after menopause. However, that same study pointed out that fluctuations of sex hormone levels during the life cycle might influence TTH as well as migraine [131].

Hormonal therapy Hormonal manipulation in elderly women cannot be considered for migraine prevention at this time. HRT is contraindicated from 10 years after menopause or in women aged 60 years or older due to its potential cardiovascular side effects [141]. No other hormonal therapy has been attempted in the prevention of migraine in elderly women. Clomiphene citrate has been used to treat chronic cluster headache and refractory primary SUNCT in single cases of elderly males [142, 143]. Clomiphene has a direct effect on hypothalamic estrogen receptors and estrogen modulates hypothalamic orexin expression. Hypothalamic estrogen receptors co-localize to orexin neurons. Therefore, clomiphene might upregulate orexin A levels, which in turn inhibits the trigeminal nucleus caudalis activity and secondarily suppresses the trigemino-autonomic reflex, preventing hypothalamic-driven headache [142]. These results are promising in considering hormonal therapies as prevention for headache disorders in elderly women. However, there are no studies to date.

Males

Migraine

Migraine is notoriously known to be two to three times more prevalent in women than in men. Migraine is characterized by its fluctuating nature, where periods of remission are interspersed by relapse, with men more likely to have longer periods of remission compared to women. This female dominance of migraine suggests that factors increasing female vulnerability and/or protecting males deserve greater focus in migraine pathophysiology [144]. Interestingly, a study has shown that male-to-female transsexuals who use antiandrogens to suppress male sex characteristics and estrogens to induce female sex characteristics have migraine rates similar to genetic females, further adding to the notion that gender-specific hormones play a role in migraine prevalence. The authors suggest that this similarity in

migraine prevalence could include structural differences in the transsexual brain or that migraine headache is part of the female gender role [145].

Animal models of migraine have attempted to investigate the gender specific difference in migraine prevalence. In an animal model of familial hemiplegic migraine type 1 (FHM1), it has been shown that orchiectomy increases susceptibility to cortical spreading depression, a response partially reversed with testosterone replacement [146]. Also, female FHM1 mutant mice were more susceptible to cortical spreading depression than males [146–148].

Another explanation for increased prevalence of migraine in women could be attributed to inherent differences in pain perception and processing. The fundamental subjectivity of pain perception complicates quantification of pain, yet it is generally accepted that women and men experience pain differently due to both biological and psychosocial traits [144]. Clinical studies are often not designed to decipher gender-specific difference [149].

Cluster headache

In contrast to migraine, cluster headache has traditionally been considered a male disease [150]. While the characteristic physical attributes of cluster headache patients could point to high testosterone levels, the exact opposite has been shown to be true [151]. Low testosterone levels in patients with episodic and chronic cluster headaches were first noted in the 1970ies and later reproduced [152–154]. Another study found low testosterone levels in the episodic but not chronic cluster headache, a difference attributed by the authors to the disruption of REM sleep [154].

The role of testosterone in cluster headache was further studied by Stillman et al. in their investigation of laboratory findings of 7 male and 2 female patients with treatment refractory cluster headache. Results of all 9 patients demonstrated low serum testosterone levels. After supplementation with either pure testosterone in the male patients or combination testosterone/estrogen therapy in the female patients, pain freedom was achieved for the first 24 h. Four male chronic cluster patients achieved headache remission. The authors concluded that abnormal testosterone levels in patients with episodic or chronic cluster headaches refractory to maximal medical management may be predictive of therapeutic response to testosterone replacement therapy [2].

Discussion

Reviewing recent literature, it becomes evident that most experimental data on the causal relationship between sex hormones and primary headaches covers women suffering from migraine in the reproductive or perimenopausal phase of their life. Particularly the effect of estrogen has been studied and has been found to be of considerable value in the pathogenesis of migraine. The estrogen withdrawal hypothesis plays a central role here, but it is assumed that this is only part of the mechanism. Some therapeutic strategies have been developed based on this knowledge. Continuous combined contraceptive therapy regimes can be considered as a treatment for menstrual migraine. However, there is currently no evidence to support the superiority of hormonal therapy over non-hormonal pharmacological treatment strategies. When using hormonal therapies in migraine patients, whether it is as a contraceptive or as a treatment, potential cardiovascular risks should be considered when deciding which type of hormones to use.

For the other primary headaches and more so ever for headaches in male patients, the role of sex hormones is vague. Is there more to know? It seems plausible that trying to uncover the effects of sex hormones on the other primary headaches may offer new insights in pathophysiological mechanisms. The more we know on this matter, the more targeted possible new therapies can be.

Conclusion

All three primary headaches, migraine, TTH, and CH, occur in both genders, but with a sex-specific prevalence. Also, headache patterns display a temporal evolution that correlates to the hormonal shifts of a life cycle. Collectively, these findings suggest that both male and female sex hormones could play an important role in the pathophysiology of primary headaches. Reviewing the available literature on this matter, we can conclude that especially the role of estrogen in female migraine patients has been well-studied. Detailed studies especially in the elderly of both sexes, in CH, and TTH are warranted in order to clearly elucidate the role of sex hormones in not just migraine, but all primary headaches.

Abbreviations

CGRP: Calcitonin gene-related peptide; CH: Cluster headache; FHM1: Familial hemiplegic migraine type 1; FSH: Follicle stimulating hormone; GABA: Gamma-aminobutyric acid; HRT: Hormonal replacement therapy; ICHD: International Classification of Headache Disorders; IHS: International Headache Society; LH: Luteinizing hormone; NMDA: N-methyl-D-aspartate; SUNCT: Short, unilateral, neuralgiform headache with conjunctival injection and tearing; TTH: Tension-type headache

Acknowledgements

This manuscript is a product of the program School of Advanced Studies promoted by the European Headache Federation (EHF-SAS).

Funding

The authors received no specific funding for this work.

Availability of data and materials

Not applicable.

Authors' contributions

All authors on behalf of European Headache Federation contributed equally to the conception, design, drafting and critical revisions of the manuscript. All authors read and approved the final manuscript. DZ, ITA, KS, NA, OR, RB,

TA are Junior Fellows of EHF-SAS and RU and MDD are Senior Fellows of EHF-SAS.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
All the authors declared no competing interests related to the contents of this review. Furthermore, all authors declare that they have received no direct or indirect payment in preparation of this manuscript.

Publisher's Note

Author details
[1]Department of Neurology, University Hospital Ghent, Corneel Heymanslaan 10, 9000 Ghent, Belgium. [2]First Moscow State Medical University, Moscow, Russia. [3]Danish Headache Center, Glostrup Hospital, Copenhagen, Denmark. [4]Dipartimento di Medicina Clinica e Molecolare, Universita degli Studi di Roma La Sapienza, Rome, Italy. [5]Department of Neurology, University of La'Aquila, L'Aquila, Italy. [6]Departmentt of Neurology, Charité Universitätsmedizin Berlin, Berlin, Germany. [7]Department of Neurosciences, Headache Center, University of Padua, Padua, Italy. [8]Neurology Department, Aeginition Hospital, National and Kapodistrian University of Athens, Athens, Greece. [9]Charite Universitatsmedizin Berlin, Berlin, Germany.

Received: 29 August 2018 Accepted: 20 September 2018
Published online: 29 November 2018

References
1. Cairns BE, Gazerani P (2009) Sex-related differences in pain. Maturitas 63: 292–296
2. Stillman MJ (2006) Testosterone replacement therapy for treatment refractory cluster headache. Headache 46:925–933
3. Silberstein SD (2000) Sex hormones and headache. Rev Neurol (Paris) 156(Suppl 4):4S30–4S41
4. Borsook D, Erpelding N, Lebel A et al (2014) Sex and the migraine brain. Neurobiol Dis 68:200–214
5. Ripa P, Ornello R, Degan D et al (2015) Migraine in menopausal women: a systematic review. Int J Womens Health 7:773–782
6. Pavlovic JM, Akcali D, Bolay H et al (2017) Sex-related influences in migraine. J Neurosci Res 95:587–593
7. Martin VT, Behbehani M (2006) Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis--part I. Headache 46:3–23
8. Martin VT, Behbehani M (2006) Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis--part 2. Headache 46:365–386
9. Bjorling EA, Singh N (2017) Exploring Temporal Patterns of Stress in Adolescent Girls with Headache. Stress Health 33:69–79
10. Aegidius KL, Zwart JA, Hagen K et al (2011) Increased headache prevalence in female adolescents and adult women with early menarche. The Head-HUNT Studies. Eur J Neurol 18:321–328
11. Martin VT, Allen JR, Houle TT et al (2017) Ovarian hormones, age and pubertal development and their association with days of headache onset in girls with migraine: An observational cohort study. Cephalalgia. https://doi.org/10.1177/0333102417706980
12. Hershey A, Horn P, Kabbouche M et al (2012) Genomic expression patterns in menstrual-related migraine in adolescents. Headache 52:68–79
13. Marcus DA (2001) Sex hormones and chronic headache in women. Expert Opin Pharmacother 2:1839–1848
14. Eren E, Yapici S, Cakir ED et al (2011) Clinical course of hyperprolactinemia in children and adolescents: a review of 21 cases. J Clin Res Pediatr Endocrinol 3:65–69
15. Catli G, Abaci A, Altincik A et al (2012) Hyperprolactinemia in children: clinical features and long-term results. J Pediatr Endocrinol Metab 25:1123–1128
16. Catli G, Abaci A, Bober E et al (2013) Clinical and diagnostic characteristics of hyperprolactinemia in childhood and adolescence. J Pediatr Endocrinol Metab 26:1–11
17. Allais G, Chiarle G, Sinigaglia S et al (2018) Menstrual migraine: a review of current and developing pharmacotherapies for women. Expert Opin Pharmacother 19:123–136
18. Martin VT, Lipton RB (2008) Epidemiology and biology of menstrual migraine. Headache 48(Suppl 3):S124–S130
19. Vincent K, Tracey I (2010) Sex hormones and pain: the evidence from functional imaging. Curr Pain Headache Rep 14:396–403
20. Craft RM (2007) Modulation of pain by estrogens. Pain 132(Suppl 1):S3–S12
21. Tassorelli C, Greco R, Allena M et al (2012) Transdermal hormonal therapy in perimenstrual migraine: why, when and how? Curr Pain Headache Rep 16:467–473
22. Horev A, Wirguin I, Lantsberg L et al (2005) A high incidence of migraine with aura among morbidly obese women. Headache 45:936–938
23. Fava A, Pirritano D, Consoli D et al (2014) Chronic migraine in women is associated with insulin resistance: a cross-sectional study. Eur J Neurol 21:267–272
24. Gupta S, Mccarson KE, Welch KM et al (2011) Mechanisms of pain modulation by sex hormones in migraine. Headache 51:905–922
25. Zacur HA (2006) Hormonal changes throughout life in women. Headache 46(Suppl 2):S49–S54
26. Warnock JK, Cohen LJ, Blumenthal H et al (2017) Hormone-Related Migraine Headaches and Mood Disorders: Treatment with Estrogen Stabilization. Pharmacotherapy 37:120–128
27. Krause DN, Duckles SP, Pelligrino DA (2006) Influence of sex steroid hormones on cerebrovascular function. J Appl Physiol (1985) 101:1252–1261
28. Miller VM, Duckles SP (2008) Vascular actions of estrogens: functional implications. Pharmacol Rev 60:210–241
29. Labastida-Ramirez A, Rubio-Beltran E, Villalon CM et al (2017) Gender aspects of CGRP in migraine. Cephalalgia. https://doi.org/10.1177/0333102417739584
30. Gruber CJ, Huber JC (2003) Differential effects of progestins on the brain. Maturitas 46(Suppl 1):S71–S75
31. Vasiadi M, Kempuraj D, Boucher W et al (2006) Progesterone inhibits mast cell secretion. Int J Immunopathol Pharmacol 19:787–794
32. Colson NJ, Lea RA, Quinlan S et al (2004) The estrogen receptor 1 G594A polymorphism is associated with migraine susceptibility in two independent case/control groups. Neurogenetics 5:129–133
33. Colson NJ, Lea RA, Quinlan S et al (2006) No role for estrogen receptor 1 gene intron 1 Pvu II and exon 4 C325G polymorphisms in migraine susceptibility. BMC Med Genet 7:12
34. Lee H, Sininger L, Jen JC et al (2007) Association of progesterone receptor with migraine-associated vertigo. Neurogenetics 8:195–200
35. Mehrotra S, Gupta S, Chan KY et al (2008) Current and prospective pharmacological targets in relation to antimigraine action. Naunyn Schmiedeberg's Arch Pharmacol 378:371–394
36. Rodriguez-Acevedo AJ, Maher BH, Lea RA et al (2013) Association of oestrogen-receptor gene (ESR1) polymorphisms with migraine in the large Norfolk Island pedigree. Cephalalgia 33:1139–1147
37. Sutherland HG, Champion M, Plays A et al (2017) Investigation of polymorphisms in genes involved in estrogen metabolism in menstrual migraine. Gene 607:36–40
38. Schurks M, Rist PM, Kurth T (2010) Sex hormone receptor gene polymorphisms and migraine: a systematic review and meta-analysis. Cephalalgia 30:1306–1328
39. Li L, Liu R, Dong Z et al (2015) Impact of ESR1 Gene Polymorphisms on Migraine Susceptibility: A Meta-Analysis. Medicine (Baltimore) 94:e0976
40. Joshi G, Pradhan S, Mittal B (2010) Role of the oestrogen receptor (ESR1 PvuII and ESR1 325 C->G) and progesterone receptor (PROGINS) polymorphisms in genetic susceptibility to migraine in a North Indian population. Cephalalgia 30:311–320
41. Parashar R, Bhalla P, Rai NK et al (2014) Migraine: is it related to hormonal disturbances or stress? Int J Womens Health 6:921–925
42. Cavestro C, Rosatello A, Marino MP et al (2006) High prolactin levels as a worsening factor for migraine. J Headache Pain 7:83–89
43. Peres MF, Sanchez Del Rio M, Seabra ML et al (2001) Hypothalamic involvement in chronic migraine. J Neurol Neurosurg Psychiatry 71:747–751
44. Glaser R, Dimitrakakis C, Trimble N et al (2012) Testosterone pellet implants and migraine headaches: a pilot study. Maturitas 71:385–388
45. Check JH, Cohen R (2013) Dihydrotestosterone may contribute to the development of migraine headaches. Clin Exp Obstet Gynecol 40:217–218
46. Macgregor EA, Frith A, Ellis J et al (2006) Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. Neurology 67:2154–2158

47. Maasumi K, Tepper SJ, Kriegler JS (2017) Menstrual Migraine and Treatment Options: Review. Headache 57:194–208
48. Martin VT, Wernke S, Mandell K et al (2005) Defining the relationship between ovarian hormones and migraine headache. Headache 45:1190–1201
49. Newman LC (2007) Understanding the causes and prevention of menstrual migraine: the role of estrogen. Headache 47(Suppl 2):S86–S94
50. Glinskii OV, Huxley VH, Glinsky VV (2017) Estrogen-Dependent Changes in Dura Mater Microvasculature Add New Insights to the Pathogenesis of Headache. Front Neurol 8:549
51. Borkum JM (2016) Migraine Triggers and Oxidative Stress: A Narrative Review and Synthesis. Headache 56:12–35
52. Macgregor EA (2009) Estrogen replacement and migraine. Maturitas 63:51–55
53. Loder E, Rizzoli P, Golub J (2007) Hormonal management of migraine associated with menses and the menopause: A clinical review. Headache 47:329–340
54. Macgregor EA (2004) Oestrogen and attacks of migraine with and without aura. Lancet Neurol 3:354–361
55. Calhoun A (2012) Combined Hormonal Contraceptives: Is It Time to Reassess Their Role in Migraine? Headache 52:648–660
56. Calhoun AH, Batur P (2017) Combined hormonal contraceptives and migraine: An update on the evidence. Clev Clin J Med 84:631–638
57. Pavlovic JM, Allshouse AA, Santoro NF et al (2016) Sex hormones in women with and without migraine: Evidence of migraine-specific hormone profiles. Neurology 87:49–56
58. Welch KMA, Brandes JL, Berman NEJ (2006) Mismatch in how oestrogen modulates molecular and neuronal function may explain menstrual migraine. Neurol Sci 27:S190–S192
59. Nappi RE, Nappi G (2012) Neuroendocrine aspects of migraine in women. Gynecol Endocrinol 28:37–41
60. Almen-Christensson A, Hammar M, Lindh-Astrand L et al (2011) Prevention of menstrual migraine with perimenstrual transdermal 17-beta-estradiol: a randomized, placebo-controlled, double-blind crossover study. Fertil Steril 96:498–U345
61. Nappi RE, Sances G, Allais G et al (2011) Effects of an estrogen-free, desogestrel-containing oral contraceptive in women with migraine with aura: a prospective diary-based pilot study. Contraception 83:223–228
62. Nappi RE, Merki-Feld GS, Terreno E et al (2013) Hormonal contraception in women with migraine: is progestogen-only contraception a better choice? J Headache Pain 14
63. Merki-Feld GS, Imthurn B, Dubey R et al (2017) Improvement of migraine with change from combined hormonal contraceptives to progestin-only contraception with desogestrel: How strong is the effect of taking women off combined contraceptives? J Obstet Gynaecol 37:338–341
64. Allais G, Gabellari IC, De Lorenzo C et al (2011) Oral contraceptives in migraine therapy. Neurol Sci 32:S135–S139
65. Smitherman TA, Kolivas ED (2010) Resolution of Menstrually Related Migraine Following Aggressive Treatment for Breast Cancer. Headache 50:485–488
66. Martin V, Wernke S, Mandell K et al (2003) Medical oophorectomy with and without estrogen add-back therapy in the prevention of migraine headache. Headache 43:309–321
67. Manzoni Gc TP (2003) Epidemiology of migraine. J Headache Pain 4(Suppl 1):s18–s22
68. Scharfman HE, Maclusky NJ (2008) Estrogen-growth factor interactions and their contributions to neurological disorders. Headache 48:S77–S89
69. Eikermann-Haerter K, Kudo C, Moskowitz MA (2007) Cortical spreading depression and estrogen. Headache 47:S79–S85
70. Finocchi C, Ferrari M (2011) Female reproductive steroids and neuronal excitability. Neurol Sci 32:S31–S35
71. Lopez-Picado A, Lapuente O, Lete I (2017) Efficacy and side-effects profile of the ethinylestradiol and etonogestrel contraceptive vaginal ring: a systematic review and meta-analysis. Eur J Contracep Repr 22:131–146
72. Bousser MG (2004) Estrogens, migraine, and stroke. Stroke 35:2652–2656
73. Aegidius K, Zwart JA, Hagen K et al (2006) Oral contraceptives and increased headache prevalence - The Head-HUNT Study. Neurology 66:349–353
74. Macgregor EA (2013) Contraception and Headache. Headache 53:247–276
75. De Icco R, Cucinella L, De Paoli I et al (2016) Modulation of nociceptive threshold by combined hormonal contraceptives in women with oestrogen-withdrawal migraine attacks: a pilot study. J Headache Pain 17
76. Allais G, Gabellari IC, Airola G et al (2009) Headache induced by the use of combined oral contraceptives. Neurol Sci 30:S15–S17
77. Loder EW, Buse DC, Golub JR (2005) Headache and combination estrogen-progestin oral contraceptives: integrating evidence, guidelines, and clinical practice. Headache 45:224–231
78. Sulak P, Willis S, Kuehl T et al (2007) Headaches and oral contraceptives: Impact of eliminating the standard 7-day placebo interval. Headache 47:27–37
79. Macias G, Merki-Feld GS, Parke S et al (2013) Effects of a combined oral contraceptive containing oestradiol valerate/dienogest on hormone withdrawal-associated symptoms: Results from the multicentre, randomised, double-blind, active-controlled HARMONY II study. J Obstet Gynaecol 33:591–596
80. Allais G, Chiarle G, Bergandi F et al (2016) The use of progestogen-only pill in migraine patients. Expert Rev Neurother 16:71–82
81. Warhurst S, Rofe CJ, Brew BJ et al (2017) Effectiveness of the progestin-only pill for migraine treatment in women: A systematic review and meta-analysis. Cephalalgia. https://doi.org/10.1177/0333102417710636
82. Schurks M, Rist PM, Bigal ME et al (2009) Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 339:b3914
83. Sacco S, Merki-Feld GS, Kl AE et al (2017) Hormonal contraceptives and risk of ischemic stroke in women with migraine: a consensus statement from the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC). J Headache Pain 18:108
84. Nobre ME, Peres MFP, Moreira PF et al (2017) Clomiphene treatment may be effective in refractory episodic and chronic cluster headache. Arq Neuro-Psiquiat 75:620–624
85. Rozen T (2008) Clomiphene citrate for treatment refractory chronic cluster headache. Headache 48:286–290
86. Bosco DLA, Mungari P (2007) SUNCT and high nocturnal prolactin levels: some new unusual characteristics. J Headache Pain 8:114–118
87. Kreitschmann-Andermahr I, Siegel S, Weber Carneiro R et al (2013) Headache and pituitary disease: a systematic review. Clin Endocrinol 79:760–769
88. Patil MJ, Henry MA, Akopian AN (2014) Prolactin receptor in regulation of neuronal excitability and channels. Channels 8
89. Bosco D, Belfiore A, Fava A et al (2008) Relationship between high prolactine levels and migraine attacks in patients with macroprolactinoma. J Headache Pain 9:103–107
90. Kallestrup MM, Kasch H, Osterby T et al (2014) Prolactinoma-associated headache and dopamine agonist treatment. Cephalalgia 34:493–502
91. Freeman EW, Sammel MD, Lin H et al (2008) Symptoms in the menopausal transition hormone and behavioral correlates. Obstet Gynecol 111:127–136
92. Allais G, Chiarle G, Bergandi F et al (2015) Migraine in perimenopausal women. Neurol Sci 36:S79–S83
93. Stewart WF, Lipton RB, Chee E et al (2000) Menstrual cycle and headache in a population sample of migraineurs. Neurology 55:1517–1523
94. Wang SJ, Fuh JL, Lu SR et al (2003) Migraine prevalence during menopausal transition. Headache 43:470–478
95. Martin VT, Pavlovic J, Fanning KM et al (2016) Perimenopause and Menopause Are Associated With High Frequency Headache in Women With Migraine: Results of the American Migraine Prevalence and Prevention Study. Headache 56:292–305
96. Harlow SD, Gass M, Hall JE et al (2012) Executive Summary of the Stages of Reproductive Aging Workshop+10: Addressing the Unfinished Agenda of Staging Reproductive Aging. J Clin Endocr Metab 97:1159–1168
97. Soules MR, Sherman S, Parrott E et al (2001) Executive summary - Stages of Reproductive Aging Workshop (STRAW). J Women Health Gen-B 10:843–848
98. Van Voorhis BJ, Santoro N, Harlow S et al (2008) The relationship of bleeding patterns to daily reproductive hormones in women approaching menopause. Obstet Gynecol 112:101–108
99. Smith OPM, Jabbour HN, Critchley HOD (2007) Cyclooxygenase enzyme expression and E series prostaglandin receptor signalling are enhanced in heavy menstruation. Hum Reprod 22:1450–1456
100. Martin VT (2008) New Theories in the Pathogenesis of Menstrual Migraine. Curr Pain Headache R 12:453–462
101. Vukovic-Cvetkovic V, Plavec D, Lovrencic-Huzjan A et al (2010) Is Iron Deficiency Anemia Related to Menstrual Migraine? - Post Hoc Analysis of an Observational Study Evaluating Clinical Characteristics of Patients with Menstrual Migraine. Acta Clin Croat 49:389–394
102. Odegard SS, Sand T, Engstrom M et al (2011) The Long-Term Effect of Insomnia on Primary Headaches: A Prospective Population-Based Cohort Study (HUNT-2 and HUNT-3). Headache 51:570–580
103. Misakian AL, Langer RD, Bensenor IM et al (2003) Postmenopausal hormone therapy and migraine headache. J Women's Health 12:1027–1036

104. Aegidius KL, Zwart JA, Hagen K et al (2007) Hormone replacement therapy and headache prevalence in postmenopausal women. The Head-HUNT study. Eur J Neurol 14:73–78
105. Nappi RE, Cagnacci A, Granella F et al (2001) Course of primary headaches during hormone replacement therapy. Maturitas 38:157–163
106. Macgregor EA, Frith A, Ellis J et al (2006) Prevention of menstrual attacks of migraine - A double-blind placebo-controlled crossover study. Neurology 67:2159–2163
107. Macgregor A (1999) Effects of oral and transdermal estrogen replacement on migraine. Cephalalgia 19:124–125
108. Macgregor EA (2012) Perimenopausal migraine in women with vasomotor symptoms. Maturitas 71:79–82
109. Neri I, Granella F, Nappi R et al (1993) Characteristics of Headache at Menopause - a Clinico-Epidemiologic Study. Maturitas 17:31–37
110. Arumugam M, Parthasarathy V (2015) Increased incidence of migraine in women correlates with obstetrics and gynaecological surgical procedures. Int J Surg 22:105–109
111. Ailani J (2010) Tension-Type Headache and Women: Do Sex Hormones Influence Tension-Type Headache? Curr Pain Headache R 14:436–440
112. Spierings ELH, Ranke AH, Honkoop PC (2001) Precipitating and aggravating factors of migraine versus tension-type headache. Headache 41:554–558
113. Zivadinov R, Willheim K, Sepic-Grahovac D et al (2003) Migraine and tension-type headache in Croatia: a population-based survey of precipitating factors. Cephalalgia 23:336–343
114. Arjona A, Rubi-Callejon J, Guardado-Santervas P et al (2007) Menstrual tension-type headache: Evidence for its existence. Headache 47:100–103
115. Oh K, Jung KY, Choi JY et al (2012) Headaches in Middle-Aged Women during Menopausal Transition: A Headache Clinic-Based Study. Eur Neurol 68:79–83
116. Lieba-Samal D, Wober C (2011) Sex Hormones and Primary Headaches Other than Migraine. Curr Pain Headache R 15:407–414
117. Ekbom K, Svensson DA, Traff H et al (2002) Age at onset and sex ratio in cluster headache: observations over three decades. Cephalalgia 22:94–100
118. Puri V, Puri S, Svojanovsky SR et al (2006) Effects of oestrogen on trigeminal ganglia in culture: implications for hormonal effects on migraine. Cephalalgia 26:33–42
119. Burger H (2008) The menopausal transition - Endocrinology. J Sex Med 5: 2266–2273
120. Van Vliet JA, Favier I, Helmerhorst FM et al (2006) Cluster headache in women: relation with menstruation, use of oral contraceptives, pregnancy, and menopause. J Neurol Neurosur Ps 77:690–692
121. Bahra A, May A, Goadsby PJ (2002) Cluster headache - A prospective clinical study with diagnostic implications. Neurology 58:354–361
122. Sharma TL (2018) Common Primary and Secondary Causes of Headache in the Elderly. Headache
123. Waters WE (1974) The pontypridd headache survey. Headache 14:81–90
124. Cook NR, Evans DA, Funkenstein HH et al (1989) Correlates of headache in a population-based cohort of elderly. Arch Neurol 46:1338–1344
125. Boardman HF, Thomas E, Croft PR et al (2003) Epidemiology of headache in an English district. Cephalalgia 23:129–137
126. Ruiz M, Pedraza MI, De La Cruz C et al (2014) Headache in the elderly: characteristics in a series of 262 patients. Neurologia 29:321–326
127. Evers S, Goadsby PJ (2003) Hypnic headache: clinical features, pathophysiology, and treatment. Neurology 60:905–909
128. Pascual J, Berciano J (1994) Experience in the diagnosis of headaches that start in elderly people. J Neurol Neurosurg Psychiatry 57:1255–1257
129. Song TJ, Kim YJ, Kim BK et al (2016) Characteristics of Elderly-Onset (>/=65 years) Headache Diagnosed Using the International Classification of Headache Disorders, Third Edition Beta Version. J Clin Neurol 12:419–425
130. Mattsson P (2003) Hormonal factors in migraine: A population-based study of women aged 40 to 74 years. Headache 43:27–35
131. Karli N, Baykan B, Ertas M et al (2012) Impact of sex hormonal changes on tension-type headache and migraine: a cross-sectional population-based survey in 2,600 women. J Headache Pain 13:557–565
132. Whitty CW, Hockaday JM (1968) Migraine: a follow-up study of 92 patients. Br Med J 1:735–736
133. Cupini LM, Matteis M, Troisi E et al (1995) Sex-hormone-related events in migrainous females. A clinical comparative study between migraine with aura and migraine without aura. Cephalalgia 15:140–144
134. Mueller L (2000) Predictability of exogenous hormone effect on subgroups of migraineurs. Headache 40:189–193
135. Granella F, Sances G, Zanferrari C et al (1993) Migraine without Aura and Reproductive Life Events - a Clinical Epidemiologic-Study in 1300 Women. Headache 33:385–389
136. Granella F, Sances G, Pucci E et al (2000) Migraine with aura and reproductive life events: a case control study. Cephalalgia 20:701–707
137. Wijman CA, Wolf PA, Kase CS et al (1998) Migrainous visual accompaniments are not rare in late life - The Framingham Study. Stroke 29:1539–1543
138. Vongvaivanich K, Lertakyamanee P, Silberstein SD et al (2015) Late-life migraine accompaniments: A narrative review. Cephalalgia 35:894–911
139. Bigal ME, Liberman JN, Lipton RB (2006) Age-dependent prevalence and clinical features of migraine. Neurology 67:246–251
140. Mattsson P (2002) Serum levels of androgens and migraine in postmenopausal women. Clin Sci 103:487–491
141. Stuenkel CA, Davis SR, Gompel A et al (2015) Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocr Metab 100:3975–4011
142. Rozen TD (2014) Complete alleviation of treatment refractory primary SUNCT syndrome with clomiphene citrate (a medicinal deep brain hypothalamic modulator). Cephalalgia 34:1021–1024
143. Rozen TD (2015) Clomiphene Citrate as a Preventive Treatment for Intractable Chronic Cluster Headache: A Second Reported Case With Long-Term Follow-Up. Headache 55:571–574
144. Loewendorf AI, Matynia A, Saribekyan H et al (2016) Roads Less Traveled: Sexual Dimorphism and Mast Cell Contributions to Migraine Pathology. Front Immunol 7
145. Pringsheim T, Gooren L (2004) Migraine prevalence in male to female transsexuals on hormone therapy. Neurology 63:593–594
146. Eikermann-Haerter K, Baum MJ, Ferrari MD et al (2009) Androgenic Suppression of Spreading Depression in Familial Hemiplegic Migraine Type 1 Mutant Mice. Ann Neurol 66:564–568
147. Moskowitz MA, Bolay H, Dalkara T (2004) Deciphering migraine mechanisms: Clues from familial hemiplegic migraine genotypes. Ann Neurol 55:276–280
148. Bolay H, Berman NEJ, Akcali D (2011) Sex-Related Differences in Animal Models of Migraine Headache. Headache 51:891–904
149. Ramirez-Maestre C, Esteve R (2014) The Role of Sex/Gender in the Experience of Pain: Resilience, Fear, and Acceptance as Central Variables in the Adjustment of Men and Women With Chronic Pain. J Pain 15:608–618
150. Rasmussen BK (1995) Epidemiology of Headache. Cephalalgia 15:45–68
151. Stillman M (2006) Steroid hormones in cluster headaches. Curr Pain Headache Rep 10:147–152
152. Kudrow L (1976) Plasma testosterone levels in cluster headache preliminary results. Headache 16:28–31
153. Nelson RF (1978) Testosterone levels in cluster and non-cluster migrainous headache patients. Headache 18:265–267
154. Romiti A, Martelletti P, Gallo MF et al (1983) Low plasma testosterone levels in cluster headache. Cephalalgia 3:41–44

Nederlandse samenvatting

De drie meest voorkomende primaire hoofdpijnsyndromen, spanningstype hoofdpijn, migraine en clusterhoofdpijn, komen zowel bij mannen als vrouwen voor. Elk hebben ze een typische geslachtsafhankelijke prevalentie. Spanningstype hoofdpijn en migraine hebben beiden een vrouwelijke predominantie, daar waar clusterhoofdpijn frequenter voorkomt bij mannen. Bijkomend wordt ook gezien dat hoofdpijnsyndromen de neiging hebben om doorheen het leven te veranderen. Vooral voor migraine zijn er data beschikbaar die aantonen dat prevalentie en karakteristieken kunnen veranderen met de leeftijd en dit vaak op momenten die gepaard gaan met belangrijke hormonale fluctuaties. Deze vaststellingen suggereren een mogelijk belangrijke rol van geslachtshormonen in de fysiopathologie bij verschillende vormen van hoofdpijn.

In deze review wordt de relevante literatuur van de laatste 20 jaar samengebracht die focust op de invloed van geslachtshormonen op migraine, clusterhoofdpijn of spanningstype hoofdpijn. Systematisch worden deze syndromen besproken in de verschillende levensfasen bij zowel man als vrouw. Bij de vrouwelijke populatie is er speciale aandacht voor de invloed van de hormonale veranderingen bij de menarche, menstruatie en perimenopauze, maar ook voor de invloed van hormonale therapie.

De beschikbare literatuur behandelt vooral vrouwen met migraine in de reproductieve of perimenopauzale fase van het leven. Voornamelijk het effect van oestrogeen is in deze context bestudeerd en de ‘estrogen withdrawal’ hypothese speelt hier een centrale, maar vermoedelijk slechts gedeeltelijke rol. Deze hypothese stelt dat het frequent voorkomen van migraine aanvallen tijdens de menstruatie kan verklaard worden door de plotse daling van de oestrogeenconcentratie die de menstruatie vooraf gaat. Op basis van de waarschijnlijke invloed van vrouwelijke geslachtshormonen zijn reeds enkele therapeutische strategieën voor menstruele migraine ontwikkeld, zoals bijvoorbeeld het continueren van een gecombineerde oestroprogestagene contraceptieve pil zonder pilvrije week. Bij het gebruik van hormonale therapie bij migraine patiënten, als hoofdpijnbehandeling of voor een andere indicatie, moet steeds aandacht worden besteed aan het mogelijke geassocieerde cardiovasculaire risico.

De literatuur omtrent de invloed van geslachtshormonen op de andere primaire hoofdpijnsyndromen en meer specifiek bij het mannelijke geslacht, is beperkt.

Bijkomende exploratie van deze zaken zou een meerwaarde kunnen zijn om het inzicht in de fysiopathologie en de daaraan verbonden mogelijke nieuwe therapeutische opties bij spanningstype hoofdpijn, clusterhoofdpijn en migraine te vergroten.