Clinical manifestations of sex hormonal influences in migraine

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Clinical Manifestations of Sex Hormonal Influences in Migraine

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Sex- and Gender-Specific Aspects of Migraine Treatment

D.S. van Casteren, E.G.M. Couturier, A. MaassenVanDenBrink

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Migraine and other headache disorders in pregnancy

D.S. van Casteren, A. MaassenVanDenBrink, G.M. Terwindt

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General Introduction

Characteristics of migraine

Migraine is a multifactorial episodic brain disorder characterized by recurrent headache attacks associated with photophobia and phonophobia and/or nausea or vomiting. Migraine headache typically lasts 4-72 hours, is unilaterally located, of pulsating quality and of moderate to severe intensity. Headache intensity often increases with physical exercise, causing avoidance of routine physical activity.[1] Approximately one-third of migraine patients experience auras prior to headaches, which are characterized by transient focal neurological disturbances, such as visual and sensory symptoms and, less frequently, dysphasia or motor symptoms. A typical aura is unilaterally located and develops gradually. Each individual aura symptom generally lasts 5-60 minutes.[2] The majority of migraine patients experience premonitory symptoms, such as fatigue, yawning, cravings for certain foods and neck stiffness up to 48 hours preceding the headache phase and, if present, the aura phase.[3,4]

Migraine susceptibility seems to be determined by a complex interaction between internal threshold modulating factors and external modifiable factors. Internal threshold modulating components mainly consist of genetic factors and sex hormonal conditions.[5,6] Examples of frequently reported external trigger factors are stress, alcohol, certain food-items, skipping meals, and weather changes.[7-10]

Sex differences in migraine prevalence

The ratio of migraine prevalence between males and females varies throughout life. In young childhood the migraine prevalence is slightly higher in boys, while the prevalence is equal in prepubertal boys and girls. This balance turns in to an increased migraine prevalence in girls after the age of menarche. Migraine peaks in prevalence in both sexes between 30 and 39 years of age.[6,11,12] During fertile years, migraine prevalence is three times higher in women than in men, with a peak prevalence of approximately 25% in women.[11] Eventually, the difference in migraine prevalence between men and women becomes smaller in the postmenopausal period, but the prevalence remains slightly higher in women even after the age of 70 years.[11,12]

Migraine prevalence in pregnancy and the postpartum period

About 60-90% of women suffering from migraine without aura report improvement of their migraine attacks during pregnancy.[13-17] Based on a prospective diary study, 47% of women

with migraine reported improvement in the first trimester, 83% in the second trimester, and 87% in the third trimester. Complete remission of migraine attacks was attained by 11% of women in the first trimester, 53% in the second trimester, and 79% in the third trimester.[13] Migraine with aura showed to be less likely to improve during pregnancy with 44%, and more often remains unchanged (49%) or even worsens (8%).[14] A small percentage of women (3-6%) experience their first migraine attack during pregnancy, which usually concerns an attack with aura during the first trimester.[15,18,19] Migraine tends to return soon after delivery. Based on the earlier mentioned prospective diary study, migraine attacks returned within 1 week in 34% of patients and within 1 month in 55%. Bottle feeding was associated with migraine recurrence within the first week in 100% of women, while this was 43% in breastfeeding women.[13] Headache activity, including severity, frequency and duration, appeared to be similar during the first 3 months after delivery in breastfeeding women compared with the second trimester of pregnancy.[20]

Hormonal fluctuations throughout the menstrual cycle

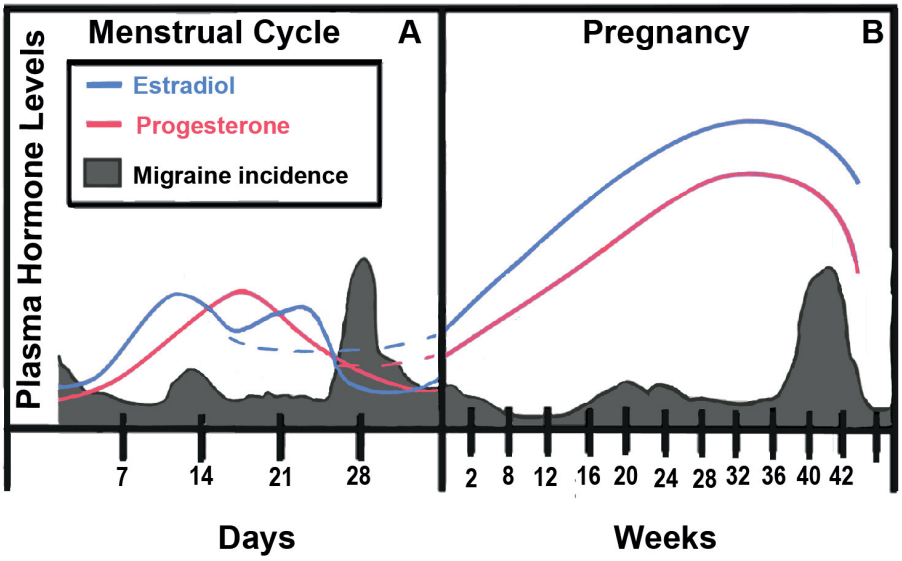
The median duration of a menstrual cycle is 28 days, and most cycle lengths are between 25 and 30 days. By definition, the first day of menstrual flow is called day +1, and there is no day 0. The menstrual cycle can be divided into two phases: [1] follicular or proliferative phase and [2] the luteal or secretory phase. The follicular phase starts on the first day of menstruation and lasts until ovulation. During this phase, the elevation of follicle stimulating hormone (FSH) causes follicles in the ovaries to grow. Ovulation, which is the release of a mature follicle, typically takes place at day 14 of the menstrual cycle and is caused by a sudden increase in luteinizing hormone (LH). This LH surge is initiated by an increase of estradiol produced by the preovulatory follicle and stimulates the synthesis of progesterone responsible for the midcycle FSH surge by luteinization of the granulosa cells. Ovulation is followed by the luteal phase. The remaining of an ovarian follicle that has released a mature oocyte during a previous ovulation is called the corpus luteum. It secretes a moderate amount of estrogen to inhibit further release of gonadotropin-releasing hormone (GnRH) and thus secretion of LH and FSH. The corpus luteum mainly secretes progesterone, which is responsible for the preparation of the uterine lining for pregnancy. If the corpus luteum is not rescued by pregnancy, progesterone withdrawal results in menses.[21]

Hormonal status during pregnancy and the postpartum period

The placenta begins to produce estradiol and progesterone during the sixth to eighth week of pregnancy. Concentrations of estradiol and progesterone continue to gradually

rise during pregnancy toward term. During the third trimester, serum concentrations of estradiol are 30-40 times higher and the level of progesterone is 20 times higher compared to peak levels of normal menstrual cycles.[22] Estrogen levels rapidly decline after delivery to reverse the physiologic changes of pregnancy, which often leads to recurrence of migraine attacks (Figure 1, panel B). Lactation inhibits ovulation by suppressing the hypothalamic–pituitary–ovarian axis, which results in stable low estrogen levels. The return of migraine in breastfeeding women may thus be delayed due to fewer estrogen fluctuations compared with non-breastfeeding women.[23] The frequency of breastfeeding may influence the duration of anovulation, which lasts on average 6 months in 70% of full breastfeeding women. The mean time to ovulation after delivery in non-breastfeeding women is 45 days.[24]

Figure 1. Hormonal fluctuations and migraine incidence throughout the menstrual cycle (panel A) and during pregnancy (panel B). Adapted from Sacco et al.[25]

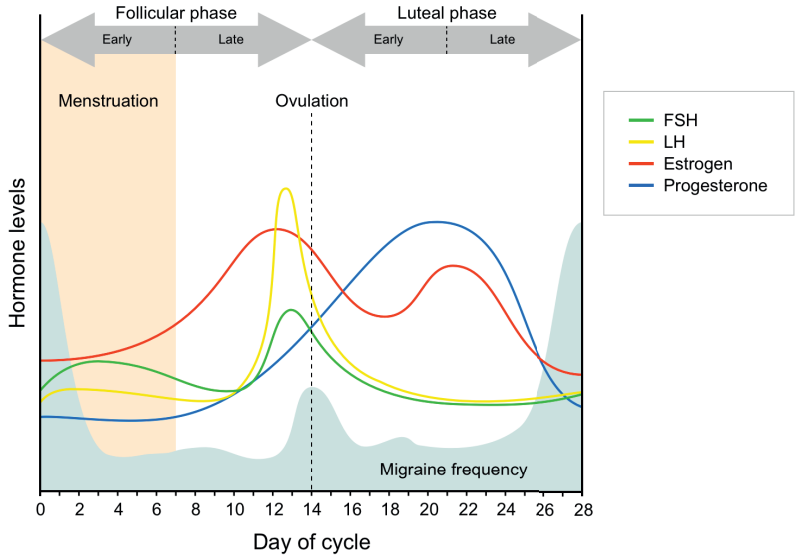


Migraine related to the menstruation

Menstruation is an important factor increasing the susceptibility for an upcoming migraine attack, with the highest risk in the period of 2 days before the menstrual period until the first 3 days of bleeding (days -2 and +3 of the menstrual cycle).[26] In approximately 55% of female migraine patients, the attacks occur not only between days -2 and +3 but can also occur at other times of the menstrual cycle.[1,27] According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), this migraine subtype

is called menstrually related migraine (MRM).[1] A small proportion of female migraine patients, approximately 5.5%, experience migraine attacks exclusively related to the menstruation.[27] This subtype is called pure menstrual migraine (PMM).[1] For research purposes, PMM and MRM are often taken together and defined as menstrual migraine (MM). Menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the use of combined oral contraceptives or cyclical hormone replacement therapy (HRT; oral or transdermal conjugated estrogens combined with cyclical oral progestogen). Thus, sex hormonal fluctuations preceding the menstruation are known to affect the susceptibility for migraine attacks, but there is a lack of understanding of the exact underlying pathophysiological mechanism. Perimenstrual migraine attacks are commonly attributed to the sudden drop in estrogen prior to menses. A similar decrease in circulating estrogen occurs at ovulation, but this decline does not seem to be consistently related to increased provocation of migraine attacks.[28,29] Therefore, increasing progesterone levels during ovulation may have migraine-preventive properties (Figure 2).

Figure 2. Hormonal fluctuations and migraine incidence throughout the menstrual cycle. Adapted from Pavlovic et al.[30]



Premenstrual syndrome and migraine

Premenstrual syndrome is characterized by recurrent, moderate-to-severe affective, physical, and behavioural symptoms that develop during the luteal phase and disappear soon after the onset of menstruation. Findings of prospective and retrospective studies

suggest that 5–8% of women with natural menstrual cycles have moderate to severe premenstrual symptoms. However, some other studies suggest that up to 20% of all women of fertile age have premenstrual complaints that could be regarded as clinically relevant.[31]

Since symptoms of premenstrual syndrome also develop during the luteal phase of the menstrual cycle and migrainous headache is often reported as physical symptom, the existence of a possible comorbidity between menstrually related migraine attacks and premenstrual syndrome has been suggested, resulting from a corresponding provoking effect of sex hormonal fluctuations. Previous studies have reported an increased risk of migraine in women with premenstrual syndrome, but results on the prevalence of premenstrual syndrome in women with migraine are inconsistent, ranging from 10-30%.[32-34] Some diary-based pilot studies suggest the existence of a possible comorbidity between menstrually related migraine attacks and premenstrual symptoms, but sample sizes were very low.[32,35,36] Two larger cross-sectional studies found no difference in occurrence of premenstrual syndrome among female migraine patients with MM and non-MM.[33,37]

Migraine during perimenopause and postmenopause

Perimenopause describes the time when a woman's menstrual cycle changes from regular to irregular as a consequence of fluctuating ovarian activity. Early menopausal transition is marked by increased variability in menstrual cycle length and is defined by a difference of 7 days or more in the length of consecutive cycles, which should occur at least twice in a period of 12 menstrual cycles. Late menopausal transition is defined by the occurrence of amenorrhea of 60 days or longer. Menopause is defined as the day of the last menstruation. Perimenopause turns into postmenopause 12 months after the last menstruation.[38] Frequently, perimenopausal migraine patients continue suffering from disabling migraine attacks despite general migraine therapies.[39,40] Fluctuations in estrogen and progesterone levels during perimenopause are associated with increased susceptibility for migraine. This effect is seen on migraine attacks without aura, but not on migraine attacks with aura.[40,41] After menopause, hormonal stability remains with high FSH levels and low estrogen and progesterone levels due to decline of the production of these hormones by the ovaries. The postmenopausal status is associated with an improvement in migraine without aura. The frequency of migraine attacks decreases, and the attacks become less severe or even disappear.[33,42,43] Migraine prevalence in spontaneous menopausal women is 10.5%, which is considerably less than the 25% prevalence that is seen in premenopausal women. However, a migraine prevalence after a surgical menopause of 27% is approximately equal

to the migraine prevalence in premenopausal women.[43,44] In conclusion, migraine usually improves after spontaneous menopause, worsens during perimenopause, and remains the same after surgical menopause.

Sex hormone levels in women with migraine

Results of studies regarding sex hormonal patterns in women with migraine are inconsistent. A previous study showed a faster decline in conjugated urinary estrogens in the late luteal phase compared to healthy controls without a significant difference in estrogen peak levels or mean daily levels between migraine patients and healthy controls.[30] Another study detected a significantly lower mean serum estradiol level on days 19-21 of the menstrual cycle of patients with MRM compared to healthy controls, while no differences in estradiol levels were present at the onset of menstruation.[45] Both studies detected no significant differences in progesterone levels during the luteal phase or at the onset of menstruation. However, other studies showed estrogen levels to be higher in women with MRM compared to controls during most phases of the menstrual cycle,[46-48] and with only small differences between MRM and non-MRM patients.[46,47] No statistically significant differences were found in serum levels of androstenedione, total testosterone, and free testosterone between postmenopausal migraine patients and healthy controls.[49] In addition, a study on salivary testosterone levels in chronic migraine patients, previously affected by medication overuse headache, compared to healthy controls detected no significant differences between both groups.[50] However, in a randomized clinical trial on the management of postmenopausal women with hormone therapy, a combination of 17β-estradiol and tibolone (a tissue-selective steroid with androgenic properties) was more effective in reducing the hours that migraine headache prohibited daily activities, compared to a combination of 17β-estradiol and estrogen-progesterone. These data suggest androgenic steroids might influence the characteristics of migraine headache.[51]

Female-specific acute migraine treatments

Patients with PMM and MRM can be treated with acutely acting drugs according to standard treatment strategy. There are no FDA- or EMA-approved treatments specifically for this group of patients. However, multiple studies have shown the effectiveness of some acutely acting treatments for perimenstrual migraine attacks.

Menstrually related migraine attacks and non-menstrually related migraine attacks can be treated with non-specific analgesics (acetaminophen and NSAIDs) and anti-emetics. However, perimenstrual attacks are generally more resistant to non-specific acute

pharmacological treatment options compared to non-menstrually related migraine attacks.[52]

Triptans (serotonin 5-$HT_{1B/1D}$ receptor agonists) are the treatment of choice for those attacks that do not respond adequately to non-specific analgesics. According to two systematic reviews on acute and prophylactic treatment options for menstrual migraine, almotriptan, sumatriptan, naratriptan, rizatriptan and zolmitriptan have shown a statistically significant higher headache response after 2 and/or 4 hours in triptan users compared to placebo.[53,54] Controlled trials with the objective to compare frovatriptan to other triptans in the acute treatment of menstrually related migraine attacks have shown equal effectiveness in headache response after 2 hours.[55-57] Recurrence rates of headache at 24 and 48 hours were significantly lower with frovatriptan (17% and 21%) than with the comparators (27% and 31%) in patients with oral contraceptive-induced menstrual migraine.[55-57] Due to its sustained antimigraine effect, frovatriptan may be most suitable for the acute treatment of menstrually related migraine attacks.

Acute treatment of migraine during pregnancy

Since women often experience relief of migraine during the second and third trimesters of pregnancy, most of acutely acting migraine medication is used in the first trimester. Preferably, pharmacological treatment of migraine attacks is prevented during this period, as the teratogenic risks of medication are typically highest during the first trimester. Although therapeutic dosages of most acute migraine medication do not increase the risk of fetus malformation or miscarriage, the safest options should be advised.[58-60]

Acetaminophen has been considered the safest acute treatment option for migraine during pregnancy. However, recent studies have raised some new concerns about its safety due to potential adverse neurodevelopmental outcomes in children who are exposed to acetaminophen for more than 28 days in utero. The EMA concluded this potential association to be based on insufficient evidence.[58,59,61]

Sumatriptan is the most hydrophilic triptan compared to other triptans, resulting in a small percentage (about 15%) of a dose crossing the placental membrane.[59] Pregnancy registry studies detected no signal of teratogenicity after maternal use of sumatriptan.[62-64] In addition, a meta-analysis and a large Norwegian Mother and Child Cohort study found no association between triptan use during pregnancy and prematurity, major congenital malformations or spontaneous abortions.[65,66] Mostly sumatriptan was used in both studies.

Only acutely acting treatments that are considered relatively safe are discussed here. Table 1 shows a summary of recommendations and restrictions regarding the use of acetaminophen, sumatriptan and other acutely acting medication during pregnancy.

Table 1. Acute medication: use during pregnancy and lactation.

	1st trimester	2nd trimester	3rd trimester	Lactation	
Acetaminophen	√	√	√	√	
NSAIDs[a]	Avoid	Avoid	Contraindicated	√	Preferably ibuprofen
Ergotamine	Contraindicated	Contraindicated	Contraindicated	Contraindicated	
Sumatriptan	?(√)	?(√)	?(√)	√	
Other triptans[b]	Insufficient data	Insufficient data	Insufficient data	?(√)	
Metoclopramide	√	√	Avoid	(√)	No more than 5 consecutive days
Domperidone	?(√)	?(√)	?(√)	(√)	No more than 7 consecutive days

√: no proof for damage; (√): data suggest unlikely to cause harm; ?(√): insufficient data, probably safe. Recommendations are based on data of several studies.[58-76] [a]Includes diclofenac, ibuprofen and naproxen. [b]Includes almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan.

Acute treatment of migraine during lactation

Most drugs transfer into breast milk to some extent. Acetaminophen has been considered a safe acutely acting treatment option for migraine during lactation, as the drug has been used by a large number of breastfeeding women without an increase in adverse effects in the infant.[58,61] Among NSAIDs, the use of ibuprofen during the lactation period is preferred as it has the lowest relative infant dose of 0.1-0.7%. In addition, ibuprofen has been studied extensively in children.[58,61]

Sumatriptan has been categorized as a safe treatment during lactation as it showed a low relative infant dose of 3.5%, even when high plasma concentrations were achieved in mothers after the use of subcutaneous sumatriptan injections.[61,67]

Only acutely acting treatments that are considered relatively safe are discussed here. Table 1 shows a summary of recommendations and restrictions regarding the use of acetaminophen, NSAIDs, sumatriptan and other acutely acting medication during lactation.

Female-specific prophylactic migraine treatments

Patients with PMM and MRM can be treated with prophylactic drugs according to standard treatment strategy. There are no FDA- or EMA-approved treatments specifically for this group of patients. However, multiple studies have shown the effectiveness of some non-specific and specific treatments in the short-term preventive treatment of perimenstrual migraine attacks.

Short-term or intermittent prophylaxis is the daily use of acute medication starting shortly before and during the menstrual period. The occurrence of perimenstrual migraine may be predictable in women with a regular menstrual cycle, allowing initiation of short-term prophylaxis a few days before the onset of an expected menstrually related migraine attack. In general, short lasting preventive medication is taken during 3-5 days before the onset of menstruation and continued during the first few days of bleeding.

Naproxen and estrogens are described as non-migraine specific pharmacological treatment options for this purpose. Naproxen 550 mg administered twice daily is the most commonly used NSAID for perimenstrual migraine prevention. However, this approach is based on a low level of evidence.[77,78] Transdermal estradiol has been studied as short-term prophylactic treatment in patients with PMM and MRM. Estradiol 1.5 mg gel showed to be associated with a higher reduction in perimenstrual migraine days in the estradiol-treated cycles compared to placebo. However, estradiol treatment was followed by deferred estrogen withdrawal, triggering an increase in post-dosing migraine during the 5 days after the gel was stopped.[79]

The highest-quality evidence for the use of triptans as short-term perimenstrual prevention exists for frovatriptan, for zolmitriptan, and to a lesser extent for naratriptan. In a systematic review, six trials involving frovatriptan, zolmitriptan and naratriptan were reviewed as short-term prevention of menstrually related migraine attacks. Frovatriptan 2.5 mg twice per day and zolmitriptan 2.5 mg three times per day appeared to be the preferred regimens.[80] Only frovatriptan 2.5 mg twice per day received a level A rate of evidence and was determined to be effective for prevention of menstrually related migraine attacks according to the guidelines of the American Academy of Neurology and American Headache Society.[81] Importantly, when using triptans as short-term prophylaxis for menstrually related attacks, the amount of medication used per month should not exceed the recommended maximum to prevent medication-overuse headache.[82]

Oral contraceptives as prophylactic migraine treatment

In patients with PMM and MRM, standard prophylactics are often considered ineffective and frequently cause side effects. Clinical data on the preventive effect of combined oral contraceptives or progestogen-only contraceptives on PMM and MRM are scarce. Mainly open-label non-comparative studies are available in the literature, therefore diminishing the strength of the evidence. In general, after introducing a combined oral contraceptive, migraine can become worse (in approximately 25%), stay the same (in approximately 50%), or become less frequent (in approximately 25%).[83] Different types and dosages of combined oral contraceptives do not have a significant influence on this results. The hormone-free interval of combined oral contraceptives can induce estrogen-withdrawal headache, which is reported in up to 70% of women using oral contraception.[84] Therefore, the effect of eliminating or shortening the hormone-free interval has been investigated in combined oral contraceptive treatments. A systematic review suggested possible benefits of an extended regimen of combined oral contraceptives in women with migraine without aura, but the quality of evidence is low.[85] However, extended use of combined oral contraceptives frequently results in breakthrough bleedings. Shortening, instead of eliminating, the hormone-free interval can minimize this risk of breakthrough bleedings. The same systematic review found two studies assessing the role of combined oral contraceptives with a shortened pill-free interval.[85] One study suggested superiority of the shortened pill-free interval treatment (24 active pills + 4 placebo pills) over the conventional one (21 active pills + 7 placebo pills) in women with PMM.[86]

The use of a daily progesterone-only pill inhibits ovulation and results in a stable estrogen production by the ovaries. Theoretically, the use of a progesterone-only pill could be effective as preventive treatment in migraine patients, especially in PMM and MRM. Four observational studies assessed the possible benefits of desogestrel 75 µg in women with migraine. Available data indicated that treatment with oral desogestrel may be associated with improvement in migraine in women with migraine with and without aura.[85]

Prophylactic treatment of migraine during pregnancy

Preferably, pharmacological preventive treatment of migraine should be avoided if a woman is intending to become pregnant, as many drugs are most dangerous during the first trimester when an existing pregnancy may not be known. Therefore, adequate preconception care is needed and women should consider discontinuation of preventive treatments during pregnancy planning. In general it is considered safe when preventive treatments are discontinued at least 5 times the half-life prior to pregnancy. Physicians

should always discuss a potential pregnancy wish with their fertile female migraine patients before starting a preventive treatment.

If preventive migraine treatment is inevitable during pregnancy, propranolol or metoprolol have often been considered the safest options, especially when used after the first trimester. However, fetal growth restriction has been reported for beta-blockers and its use should be stopped prior to labor to avoid reduced uterine contraction and fetal bradycardia. Infants should be monitored for bradycardia, hypotension and hypoglycemia after exposure to propranolol in utero.[58,61,76]

Although there is some controversy on the efficacy of amitriptyline as prophylactic migraine treatment, a causal relationship between reported teratogenic effects and maternal amitriptyline use has not been established.[58] However, the use of amitriptyline should be avoided during the third trimester because neonatal effects, including preterm birth, respiratory distress, drowsiness and hypoglycaemia have been reported.[61,76]

Botulinum toxin A is widely used as treatment of chronic migraine, but its use during pregnancy should be avoided as no adequate and well-controlled studies in humans are available.[58] The efficacy of calcitonin gene-related peptide (CGRP) (-receptor) monoclonal antibodies has been demonstrated for the preventive treatment of migraine in adults. Considerations related to the use of CGRP (-receptor) monoclonal antibodies in human pregnancies should be evaluated.

Table 2 shows a summary of recommendations and restrictions regarding the use of preventive medication during pregnancy.

Table 2. Preventive medication: use during pregnancy and lactation.

	1st trimester	2nd trimester	3rd trimester	Lactation
Propranolol	Avoid	?(√)	?(√)	(√)
Metoprolol	Avoid	?(√)	?(√)	(√)
Candesartan	Contraindicated	Contraindicated	Contraindicated	?(√)
Topiramate	Contraindicated	Contraindicated	Contraindicated	Insufficient data
Valproic acid	Contraindicated	Contraindicated	Contraindicated	Avoid
Amitriptyline	(√)	(√)	Avoid	(√)
Botulinum toxin A	Insufficient data	Insufficient data	Insufficient data	Insufficient data
CGRP(-receptor) monoclonal antibodies	Insufficient data	Insufficient data	Insufficient data	Insufficient data

√: no proof for damage; (√): data suggest unlikely to cause harm; ?(√): insufficient data, probably safe. Recommendations presented in this table are based on data of several studies and only apply when the use of a preventive treatment for migraine is inevitable during pregnancy and lactation.[58,61,75,76,87,88]

Prophylactic treatment of migraine during lactation

The use of propranolol and metoprolol as prophylactic migraine treatment are considered compatible with breastfeeding. Propranolol is preferred due to a low milk/plasma ratio (0.5), resulting in a low infant dose. Additionally, propranolol has shown least pediatric adverse events with various studies. However, infants should be monitored for hypoglycemia and the use of propranolol is contraindicated in mothers with asthma.[58,61] Infant observation for hypoglycemia, hypotension and bradycardia is advised when mothers are using metoprolol during lactation.[58,76]

Although amitriptyline concentrations in breast milk are similar to plasma levels, the use of amitriptyline during lactation has been categorized as relatively safe as no serious pediatric adverse effects are reported in several studies. However, infant monitoring for symptoms of lethargy, dry mouth, constipation and urinary retention should be considered.[58,75,76]

Only preventive treatments that are considered relatively safe are discussed here. Table 2 shows a summary of recommendations and restrictions regarding the use of beta-blockers, amitriptyline and other preventive medication during lactation.

Aims of the Thesis

In this thesis, clinical manifestations of sex hormonal influences in migraine are investigated to increase the understanding of the role of sex hormones and ultimately contribute to the effectuation of sex-specific migraine treatment approaches. The described studies can be divided into two main parts. **Part I** describes studies examining clinical sex differences in migraine. **Part II** describes studies focussing on clinical female-specific characteristics of migraine.

Part I: Clinical sex differences in migraine

Chapter 2 describes a systematic review and meta-analysis aiming to examine the effect of sex on clinical response to triptans and to determine whether these differences are related to sex-specific pharmacokinetics of triptans. In **Chapter 3,** sex differences in the prevalence of migraine trigger factors are evaluated, aiming to determine whether differences between men and women affect the potential of external trigger factors to provoke migraine attacks.

Part II: Clinical female-specific characteristics of migraine

Chapter 4 introduces a self-developed time-locked electronic diary (E-diary), including an automated algorithm differentiating headache and migraine days. The implementation of E-diaries aims to fulfill the need for a high standard in clinical practice and in research regarding the reliability of data on migraine-related outcomes, including the association between migraine attacks and the menstruation. In **Chapter 5**, a prospective E-diary study is described, comparing migraine characteristics between menstrually related migraine attacks and non-menstrually related migraine attacks. In addition, the prevalence of premenstrual syndrome as comorbidity in women with migraine is determined. A large sample of female migraine patients is included in this study, aiming to provide conclusive results since findings of previous smaller diary-based studies and retrospective cross-sectional studies have been inconsistent. In **Chapter 6**, a case-control study is presented, comparing jealousy levels within romantic relationships between women with migraine and non-migrainous controls. Estrogen influences susceptibility to migraine attacks and also has been suggested to affect jealousy in romantic relationships in women.

Chapter 7 provides a general discussion of the thesis and suggestions for future research. Finally, the thesis is summarized in **Chapter 8**.

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PART I

Clinical sex differences in migraine

CHAPTER 2

Sex differences in response to triptans: A systematic review and meta-analysis

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Abstract

Objective To examine the effect of sex on clinical response to triptans in migraine and to determine whether these differences are related to pharmacokinetics of triptans in men and women, we performed a systematic review and meta-analysis.

Methods We searched clinical trials distinguishing clinical response to or pharmacokinetic parameters of triptans between sexes in PubMed, MEDLINE, Cochrane Library, Embase and Web of Science up to Dec 12, 2019. Analysis was based on data extracted from published reports. Male-to-female pooled risk ratios (RR) were calculated for clinical outcomes and pooled ratio of means (RoM) for pharmacokinetic outcomes using random-effects models.

Results Of 1188 publications on clinical trials with triptans, 244 were identified with sex-related search terms. Only 19 publications presented sex-specific results, comprising n = 2280 men and n = 13899 women. No sex differences were revealed for 2-hour headache and pain-free responses, but men had a lower risk for headache recurrence (male-to-female RR 0.64, 95% confidence interval [CI]: 0.55-0.76, Q = 0.81) and adverse events (RR 0.82, 95% CI: 0.72-0.93, Q = 4.93). Men had lower drug exposure with lower area under the curve (RoM 0.69, 95% CI: 0.60-0.81, Q = 18.06) and peak drug concentration (RoM 0.72, 95% CI: 0.64-0.82, Q = 8.24) than women.

Conclusions Remarkably few publications about sex differences in triptan response are available. The limited number of eligible studies show sex differences in adverse event frequency, which may be partly because of drug exposure differences. This higher drug exposure in women is not reflected in different response rates. Despite higher exposure, women have higher headache recurrence rates possibly because of longer attack duration related to sex hormonal changes.

Introduction

Migraine is a common disabling episodic brain disorder, affecting 3 times more women than men.[1] In both sexes, triptans (serotonin 5-$HT_{1B/1D}$ receptor agonists) are the most widely prescribed acute migraine-specific treatments. In contrast to clinical trials in general, where most men are included,[2,3] most trials investigating effectiveness of triptans are performed with approximately 80% women. Because low numbers of men are included, the statistical power to study sex differences in triptan response is limited in individual studies.

Differences between men and women in pharmacokinetics, drug safety and efficacy may be affected by biological components but also behavioral, social, environmental and cultural factors. Because most studies only use a dichotomous variable to distinguish men from women without further distinguishing gender role identity, we use "sex" to describe differences between men and women.

Researchers in other neurologic fields, for example, stroke, multiple sclerosis, and Alzheimer's disease, have also noticed that many clinical trials were not designed to detect sex differences.[4-7] Because sex differences in migraine prevalence are even more striking, there is a clinical need to explore effects of sex on response to antimigraine treatments, starting with the most widely used triptans.

With this systematic review and meta-analysis, we investigated whether sex and sex-related differences in pharmacokinetics are determinants in triptan response. It has been debated whether sex differences in triptan exposure are important for efficacy, although subcutaneous sumatriptan showed highest peak concentrations and bioavailability combined with the most effective response.[8] Taken together, clarity on potential important sex differences in triptan response and its possible association to sex-specific pharmacokinetics is needed.

Methods

Search strategy and selection criteria

Procedures used in this systematic review and meta-analysis were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[9] A research protocol was written before the start of the study (ZonMw nr. 849100004).

We performed an electronic search for published studies with a last update on December 12, 2019 in PubMed, MEDLINE, EMBASE, Web of Science and the Cochrane Library on clinical trials distinguishing clinical response to triptans for sex or pharmacokinetic parameters of triptans for sex. The search was set up with the assistance of research librarians at the Leiden University Medical Center. The strategy for PubMed is available in figure e-1, doi:10.5061/dryad.6djh9w0zb. In addition, we performed a broad search on clinical trials with triptans in PubMed to demonstrate the attention that has been paid to triptans in general.

Study selection was independently performed by 2 investigators (D.S.v.C. and G.M.T.). Disagreement was resolved by dialogue. We included double-blind randomized controlled trials, randomized crossover trials, open-label trials, and prospective observational studies. Case reports, meeting abstracts, editorials, commentaries, articles with a pediatric population (age <18 years), and articles with incomplete information were not eligible. There were no language or date restrictions. Reference lists of included articles were examined to identify studies that might have been missed by the initial database search.

Data extraction and risk of bias assessment

Data were extracted from all eligible studies using a standardized form. Information was extracted on the following: (1) study design, (2) study population characteristics (sample size, sex, and migraine subtype), (3) type and dose of triptan(s), (4) reported estimates on clinical response outcomes of interest -- headache response after 2 hours, pain free response after 2 hours, headache recurrence within 24 or 48 hours, and adverse event frequency -- and (5) reported estimates on pharmacokinetic parameters of interest -- peak drug concentration (C_{max}), area under the curve from zero to infinite time ($AUC_{0-\infty}$), bioavailability (F), time to reach peak plasma concentration (T_{max}), plasma half-life time ($T_{½}$), and renal clearance (CL_r). The risk of bias of each included study was assessed using the critical appraisal tool -- Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument for (pseudo) randomized controlled trials. For all studies, each domain was assigned a score of high, low, or unclear risk of bias. The risk of publication bias was

assessed by visual inspection of funnel plots representing effect estimates on the *X*-axis and standard errors of the effect estimates on the *Y*-axis.

Data analysis

For each clinical response outcome male-to-female pooled risk ratios (RRs) with a 95% confidence interval (CI) were used as the main estimated effect measure. For quantitative syntheses, the Mantel-Haenszel method was applied. For the investigation of sex differences in pharmacokinetic outcomes pooled ratio of means (RoMs) were calculated. A formula described by Friedrich et al.[10] was used to calculate corresponding 95% CIs. For quantitative syntheses of pooled RoMs, the inverse variance method was used. We would have preferred to perform pooled analyses for the different outcome measures separately per triptan. However, because of a limited number of eligible studies per individual triptan, we chose to combine data on different triptans. Especially, sex differences on $T_{½}$ would preferably be calculated separately for different triptans to take relevant differences in drug metabolism into account. As only data of $T_{½}$ on frovatriptan and zolmitriptan were available separated by sex, which are both mainly metabolized by CYP1A2,[11,12] we also chose to perform pooled analyses for these 2 drugs. Furthermore, study arms closest to therapeutic doses were selected from cross-sectional studies to avoid pooling across the same participants. Random-effects models were used to anticipate on clinical between-study heterogeneity. Statistical heterogeneity of the effect between studies was assessed using the χ^2 test of Q. Analyses were conducted using Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A 2-sided *p*-value of ≤ 0.05 was considered statistically significant.

Data Availability Statement

Additional data (table e-1, table e-2, figure e-1, and figure e-2, doi:10.5061/dryad.6djh9w0zb) are available from Dryad**.** Data not published within the article will be shared by request from an investigator.

Results

A search for publications on clinical trials with triptans resulted in 1188 publications, of which 244 remained after adding sex- and gender-related search terms (see flowchart figure 1). Most of these studies were excluded because of the lack of distinguished results for men and women. Sex-specific results were presented in 19 publications, and these were

considered eligible for inclusion in the meta-analysis -- 10 publications with 2187 men and 13805 women concerning clinical response outcome measurements and 9 publications with 93 men and 94 women on pharmacokinetic outcomes.

Six of the included publications on clinical response outcome measurements presented data obtained from multiple trials. In 3 publications, the results on clinical response outcomes were pooled across treatments with different triptans (eletriptan 40/80 mg, sumatriptan 100 mg, rizatriptan 10 mg, zolmitriptan 2.5 mg, almotriptan 12.5 mg). Numbers of participants ranged from 280 to 3714 for women and from 33 to 591 for men, with an 80% female participation frequency. The age of included participants ranged from 18 to 78 years, with a mean age of approximately 40 years. Follow-up duration varied from a single attack treatment to a follow-up of 12 months. From one study, a subgroup was excluded to prevent heterogeneity because it investigated the effect of previous opioid use on response.[13] Sex division in the studies on pharmacokinetic parameters of triptans was nearly equal, with numbers ranging from 6 to 17 per group. The age of included participants in the pharmacokinetic studies also ranged from 18 to 78 years, with a mean age of approximately 35 years. In one study, hypertensive participants received antihypertensive treatment.[14] Table 1 shows characteristics of included studies (for full description see table e-1, doi:10.5061/dryad.6djh9w0zb). The risk of bias of individual publications on clinical response outcomes was mixed with an overall high risk of bias of open-label studies. Blinding of participants, allocators, and outcome assessors was considered to have less influence on the overall risk of bias of studies on pharmacokinetic outcomes (for overview of risk of bias assessments see figure e-2, doi:10.5061/dryad.6djh9w0zb).

Clinical response outcome measurements

The corresponding forest plots and references are shown in figure 2. Sex-specific information on headache response 2 hours after triptan intake (defined as reduction in headache intensity from moderate/severe before treatment to mild/no pain 2 hours after treatment) was reported in 6 studies. No sex differences were revealed for the 2-hour headache response (male-to-female RR 1.04, 95% CI: 0.98-1.11, $p = 0.19$, $Q = 12.16$). Four studies reported sex-specific information on pain-free response 2 hours after the intake of a triptan (defined as a headache reduction of any intensity before treatment to no pain 2 hours after treatment). Men and women had an equal pain-free 2-hour response (male-to-female RR 1.01, 95% CI: 0.96-1.07, $p = 0.68$, $Q = 0.95$). Men had a lower risk for headache recurrence (defined as the return or worsening of headache within 24-48 hours after an initial 2-hour headache response) (3 studies, male-to-female RR 0.64, 95% CI: 0.55-0.76, p

< 0.001, Q = 0.81). No sex-specific results were available on sustained pain-free response (defined as freedom from pain with no recurrence or use of rescue medication 2-24 hours post dose). Four studies presented distinguished data on the frequency of adverse events for men and women. Men had a lower adverse event frequency after the intake of triptans compared with women (male-to-female RR 0.82, 95% CI: 0.72-0.93, p = 0.002, Q = 4.93). Most frequently reported adverse events were asthenia, nausea, somnolence, dizziness, paraesthesia, dry mouth, and warm sensations. A χ^2 test of Q for statistical heterogeneity of the effect between studies was only statistically significant for the 2-hour headache response (p = 0.03) (figure 2). Except for the 2-hour headache response, corresponding funnel plots showed an equal distribution of number of studies on both sides of the pooled RR.

Figure 1. Flowchart of the publication selection process.

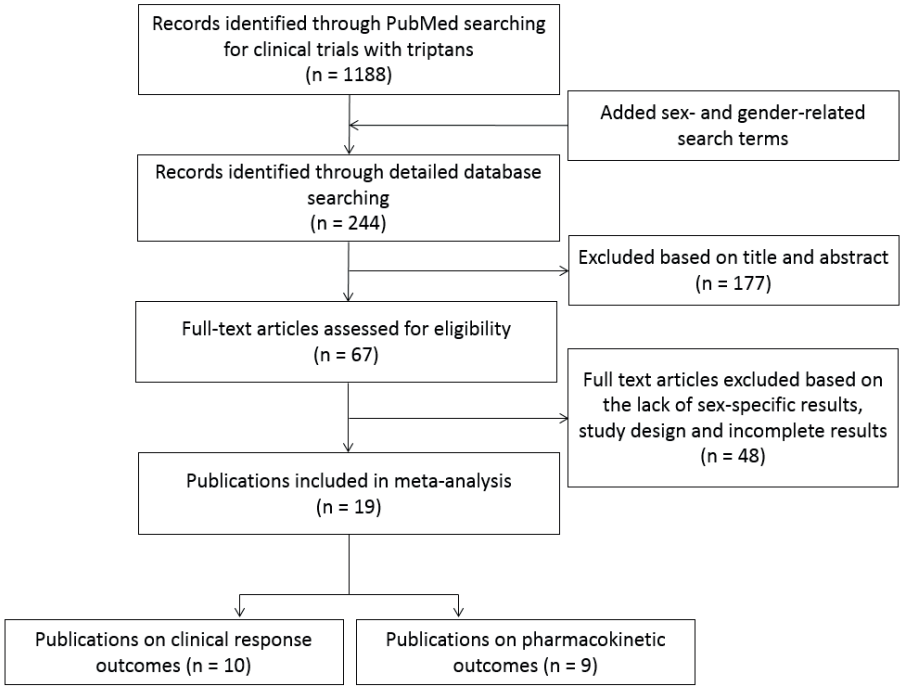


Table 1. Summary characteristics of included studies.

Studies on clinical response outcomes	Publications (n = 10)	Studies on pharmacokinetic outcomes	Publications (n = 9)
Publication year		Publication year	
≤ 2000	5 (50%)	≤ 2000	6 (67%)
2001 – 2010	4 (40%)	2001 – 2010	3 (33%)
2011 – 2018	1 (10%)	2011 – 2018	0 (0%)
Study design		Study design	
Randomized double-blind placebo-controlled study	5 (50%)	Randomized double-blind placebo-controlled study	2 (22%)
Randomized double-blind controlled crossover study	1 (10%)	Randomized double-blind placebo-controlled crossover study	2 (22%)
Non-randomized open-label crossover study	1 (10%)	Randomized open-label crossover study	4 (44%)
Uncontrolled open-label study	2 (20%)	Uncontrolled open-label study	1 (11%)
Prospective observational study	1 (10%)		
Participants		Participants	
Percentage women included > 80%	10 (100%)	Percentage women included 50%	8 (89%)
Migraine without aura + migraine with aura	10 (100%)	Percentage women included 50-55% Healthy volunteers	1 (11%) 9 (100%)
Intervention		Intervention	
Almotriptan (12.5 mg)	1 (10%)	Frovatriptan (2.5 and 40 mg)	1 (11%)
Rizatriptan (10 mg)	1 (10%)	Rizatriptan (2.5, 5, 10, and 15 mg)	3 (33%)
Sumatriptan nasal spray (10 and 20 mg) Zolmitriptan (2.5 and 5 mg)	1 (10%) 4 (40%)	Zolmitriptan (2.5, 5, 10, 15, and 20 mg)	5 (56%)
Combination of triptans	3 (30%)		

Pharmacokinetic outcomes

The corresponding forest plots and references are shown in figure 3. Men had a lower C_{max} (8 studies, RoM 0.72, 95% CI: 0.64-0.82, $p < 0.001$, $Q = 8.24$) and $AUC_{0-\infty}$ (9 studies, RoM 0.69, 95% CI: 0.60-0.81, $p < 0.001$, $Q = 18.06$) than women for frovatriptan, zolmitriptan, and rizatriptan. A pooled analysis on $T_{½}$ for frovatriptan and zolmitriptan showed no sex difference (5 studies, RoM 0.93, 95% CI: 0.80-1.08, $p = 0.34$, $Q = 5.59$). A χ^2 test of Q was only statistically significant for $AUC_{0-\infty}$ ($p = 0.02$) (figure 3). All corresponding funnel plots showed an equal distribution of number of studies on both sides of the pooled RoMs.

Discussion

This systematic review and meta-analysis show that remarkably few publications about sex differences in triptan response are available. Based on the available data, sex differences in adverse event frequency were shown, with men less prone for adverse events, which may be partly because of drug exposure differences. This higher drug exposure in women is not reflected in differences in response rates. Despite higher triptan exposure, women have higher headache recurrence rates possibly because of a longer attack duration related to sex hormonal changes.

In contrast to clinical trials that investigate the effectiveness of triptans, where most women are included, sexes were equally distributed in trials regarding pharmacokinetics of triptans. We observed no sex differences in headache and pain-free response after 2 hours for triptans, which is in line with a prospective open-label study in which no difference in the time to reach pain freedom were found between men and women for acute medication in general.[15]

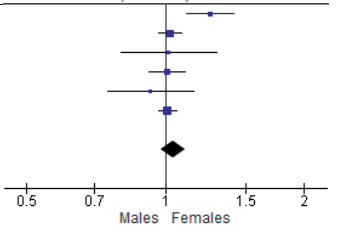
By contrast, women had a higher adverse event frequency compared with men. Using the GRADE criteria (table e-2, doi:10.5061/dryad.6djh9w0zb), we assessed the certainty of this evidence to be moderate. Women generally tend to report adverse drug reactions more frequently than men, which may be related to both biological and social/cultural differences.[16,17] In our study, the sex difference in adverse event frequency may be partly explained by a higher exposure to the drug in women, which seemed from higher C_{max} and $AUC_{0-\infty}$ values for frovatriptan, zolmitriptan, and rizatriptan. The higher drug exposure seems to exist independent of sex differences in body weight because C_{max} and $AUC_{0-\infty}$ for frovatriptan 2.5 mg are shown to be higher in women when assessing results normalized to body weight.[12] This also applies to various other drugs, such as levodopa and sertraline, of which a higher drug exposure in women may only be partially explained by their lower body weight.[18,19] Therefore, researchers and clinicians should be aware of additional factors leading to a higher drug exposure, and potentially more adverse events, in women. The higher triptan exposure in women might probably be explained by a higher bioavailability because of lower first-pass metabolism or because of alterations in receptor number or receptor binding.[12,20-22] In addition, renal clearance of rizatriptan and zolmitriptan seems to be higher in men than in women.[23-25]

Figure 2. Forest plots of the clinical response outcomes.

A. Headache response after 2 hours

		Males		Females				
	Triptan, dosage	Events	Total	Events	Total	Weight	Risk Ratio, 95% CI	Risk Ratio M-H, Random, 95% CI
Ashford et al. 1998[45]	Sumatriptan nasal spray 20 mg	98	136	486	844	14.6%	1.25 [1.11, 1.41]	
Cady et al. 1998[40]	Zolmitriptan 5 mg	239	288	1433	1769	26.2%	1.02 [0.97, 1.08]	
Franconi et al. 2014[47]	Frovatriptan 2.5 mg	37	66	154	280	5.4%	1.02 [0.80, 1.29]	
Pascual et al. 2001[44]	Almotriptan 12.5 mg	79	93	563	669	19.1%	1.01 [0.92, 1.11]	
Schoenen et al. 1997[43]	Zolmitriptan 2.5 mg	38	64	272	425	6.4%	0.93 [0.75, 1.15]	
Tuchman et al. 1999[41]	Zolmitriptan 2.5 mg	298	347	1829	2152	28.4%	1.01 [0.96, 1.06]	
Total (95% CI)			994		6139	100%	1.04 [0.98, 1.11]	
Total events		789		4737				

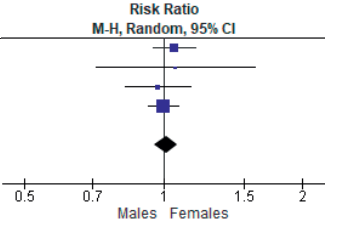
Heterogeneity: Tau² = 0.00; Chi² = 12.16, df = 5 (P = 0.03); I² = 59%
Test for overall effect: Z = 1.30 (P = 0.19)



B. Pain free response after 2 hours

		Males		Females				
	Triptan, dosage	Events	Total	Events	Total	Weight	Risk Ratio, 95% CI	Risk Ratio M-H, Random, 95% CI
Cady et al. 1998[40]	Zolmitriptan 5 mg	167	288	973	1769	28.8%	1.05 [0.95, 1.17]	
Franconi et al. 2014[47]	Frovatriptan 2.5 mg	21	66	84	280	2.1%	1.06 [0.71, 1.58]	
Ho et al. 2009[13]	Rizatriptan 10 mg	97	237	646	1538	12.3%	0.97 [0.83, 1.15]	
Tuchman et al. 1999[41]	Zolmitriptan 2.5 mg	239	347	1485	2152	56.8%	1.00 [0.92, 1.08]	
Total (95% CI)			938		5739	100.0%	1.01 [0.96, 1.07]	
Total events		524		3188				

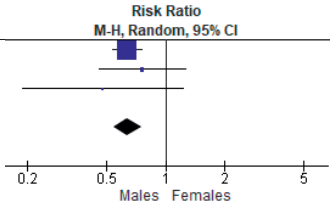
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.68)



C. Headache recurrence rate after 24 hours or 48 hours

		Males		Females			Risk Ratio,
	Triptan, dosage	Events	Total	Events	Total	Weight	95% CI
Dodick et al. 2008[46]	Eletriptan, sumatriptan, placebo	113	591	1114	3714	86.7%	0.64 [0.54, 0.76]
Franconi et al. 2014[47]	Frovatriptan 2.5 mg	14	66	78	280	10.3%	0.76 [0.46, 1.26]
Sheftell et al. 2010[48]	Triptans in general	4	33	82	326	3.0%	0.48 [0.19, 1.23]
Total (95% CI)			690		4320	100%	0.64 [0.55, 0.76]
Total events		131		1274			

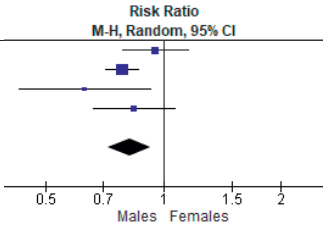
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 5.36 (P < 0.00001)



D. At least one adverse event

		Males		Females			Risk Ratio,
	Triptan, dosage	Events	Total	Events	Total	Weight	95% CI
Ashford et al. 1998[45]	Sumatriptan nasal spray 20 mg	64	140	418	871	25.3%	0.95 [0.79, 1.16]
Cady et al. 1998[40]	Zolmitriptan 5 mg	176	288	1380	1769	46.6%	0.78 [0.71, 0.86]
Edmeads et al. 1997[42]	Zolmitriptan 2.5 mg	19	63	239	498	9.0%	0.63 [0.43, 0.93]
Pascual et al. 2001[44]	Almotriptan 12.5 mg	41	93	350	669	19.1%	0.84 [0.66, 1.07]
Total (95% CI)			584		3807	100.0%	0.82 [0.72, 0.93]
Total events		300		2387			

Heterogeneity: Tau² = 0.01; Chi² = 4.93, df = 3 (P = 0.18); I² = 39%
Test for overall effect: Z = 3.14 (P = 0.002)

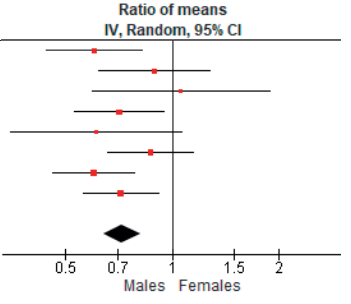


Headache response after 2 hours (A), pain-free response after 2 hours (B), headache recurrence rate after 24 hours or 48 hours (C), and the incidence of at least one adverse event after the intake of a triptan in male and female migraine patients (D). M-H = Mantel-Haenszel method; random = random effects model. The squares represent effect sizes of the individual studies (size reflects the weight of the study) and the horizontal lines indicate the 95% confidence intervals (CI). The filled diamonds represent the overall effect size (horizontal width indicates the 95% CI).

Figure 3. Forest plots of pharmacokinetic outcomes.

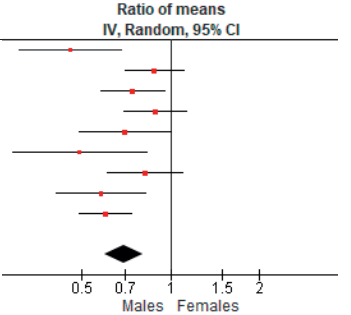
A. C_{max}, ng/ml	Triptan, dosage	Ln[Ratio of means]	Total	Total	Weight	Ratio of means, 95% CI
Buchan et al. 2002[12]	Frovatriptan 2.5 mg	-0.5037	6	6	13.2%	0.60 [0.44, 0.83]
Lee et al. 1999[23]	Rizatriptan 10 mg	-0.1154	12	12	10.4%	0.89 [0.62, 1.28]
Musson et al. 2001[24]	Rizatriptan 10 mg	0.0562	8	8	4.3%	1.06 [0.59, 1.88]
Peck et al. 1998[25]	Zolmitriptan 5 mg	-0.3425	12	12	14.7%	0.71 [0.53, 0.95]
Seaber et al. 1997[21]	Zolmitriptan 10 mg	-0.4943	6	6	4.7%	0.61 [0.35, 1.06]
Seaber et al. 1998[22]	Zolmitriptan 2.5 mg	-0.1393	10	10	16.1%	0.87 [0.66, 1.15]
Smith et al. 1998[14]	Zolmitriptan 5 mg	-0.5108	16	17	17.1%	0.60 [0.46, 0.78]
Yates et al. 2002[11]	Zolmitriptan 2.5 mg	-0.3352	15	15	19.5%	0.72 [0.56, 0.91]
Total (95% CI)			85	86	100.0%	0.72 [0.64, 0.82]

Heterogeneity: Tau² = 0.00; Chi² = 8.24, df = 7 (P = 0.31); I² = 15%
Test for overall effect: Z = 5.15 (P < 0.00001)



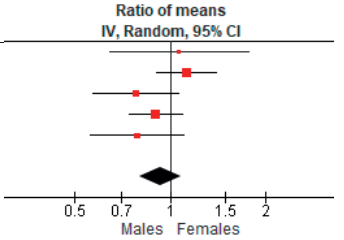
B. $AUC_{0-\infty}$, ng/h/ml	Triptan, dosage	Ln[Ratio of means]	Males Total	Females Total	Weight	Ratio of means, 95% CI
Buchan et al. 2002[12]	Frovatriptan 2.5 mg	-0.7844	6	6	8.4%	0.46 [0.31, 0.68]
Goldberg et al. 2000[49]	Rizatriptan 10 mg	-0.125	8	8	13.8%	0.88 [0.70, 1.12]
Lee et al. 1999[23]	Rizatriptan 10 mg	-0.298	12	12	13.1%	0.74 [0.58, 0.95]
Musson et al. 2001[24]	Rizatriptan 10 mg	-0.1157	8	8	13.3%	0.89 [0.70, 1.14]
Peck et al. 1998[25]	Zolmitriptan 10 mg	-0.3567	12	12	9.5%	0.70 [0.49, 1.00]
Seaber et al. 1997[21]	Zolmitriptan 10 mg	-0.7133	6	6	5.8%	0.49 [0.29, 0.83]
Seaber et al. 1998[22]	Zolmitriptan 2.5 mg	-0.1984	10	10	11.4%	0.82 [0.61, 1.10]
Smith et al. 1998[14]	Zolmitriptan 5 mg	-0.5447	16	17	9.8%	0.58 [0.41, 0.82]
Yates et al. 2002[11]	Zolmitriptan 2.5 mg	-0.5067	15	15	14.9%	0.60 [0.49, 0.74]
Total (95% CI)			93	94	100.0%	0.69 [0.60, 0.81]

Heterogeneity: Tau² = 0.03; Chi² = 18.06, df = 8 (P = 0.02); I² = 56%
Test for overall effect: Z = 4.82 (P < 0.00001)



C. $T_{1/2}$, h	Triptan, dosage	Ln[Ratio of means]	Males Total	Females Total	Weight	Ratio of means, 95% CI
Buchan et al. 2002[12]	Frovatriptan 2.5 mg	0.0641	6	6	7.8%	1.07 [0.64, 1.76]
Peck et al. 1998[25]	Zolmitriptan 10 mg	0.1222	12	12	28.3%	1.13 [0.91, 1.40]
Seaber et al. 1997[21]	Zolmitriptan 10 mg	-0.2485	6	6	17.1%	0.78 [0.57, 1.07]
Seaber et al. 1998[22]	Zolmitriptan 2.5 mg	-0.1054	10	10	31.8%	0.90 [0.74, 1.09]
Smith et al. 1998[14]	Zolmitriptan 10 mg	-0.2384	16	17	15.0%	0.79 [0.56, 1.11]
Total (95% CI)			50	51	100.0%	0.93 [0.80, 1.08]

Heterogeneity: Tau² = 0.01; Chi² = 5.59, df = 4 (P = 0.23); I² = 28%
Test for overall effect: Z = 0.95 (P = 0.34)



Peak drug concentration (Cmax, ng/ml) (A), area under the curve from time zero to infinite time (AUC0-∞, ng/h/ml) (B) and plasma half-life times (T1/2) (C). IV = inverse variance method; random = random effects model. The squares represent effect sizes of the individual studies (size reflects the weight of the study) and the horizontal lines indicate the 95% confidence intervals (CI). The filled diamonds represent the overall effect size (horizontal width indicates the 95% CI). There are a few minor discrepancies with the original studies, at the most two hundredths of decimals, in the calculation of the ratio of means and upper/lower limit of the 95% CIs because of differences in the rounding of decimals.

We expected $T_{½}$ for frovatriptan and zolmitriptan to be higher in women because both triptans are mainly metabolized by CYP1A2, which has a higher activity in men.[11,12,26] Surprisingly, no sex differences were revealed on $T_{½}$ for frovatriptan and zolmitriptan. In addition, 2 independent studies did not find sex differences for $T_{½}$ for N-desmethylzolmitriptan, the most active metabolite of zolmitriptan.[14,22] A possible explanation for this finding is the fact that a substantial proportion of female participants in the studies used an oral contraceptive pill. As ethinyl steroid-containing oral contraceptive pills are inhibitors of CYP1A2,[27] this usage might have decreased the clearance of frovatriptan and zolmitriptan in these female participants.

Contrary to what was to be expected based on the higher drug exposure, women did not have higher response rates to triptans and experienced even higher headache recurrence rates compared with men (evidence estimated as moderate based on GRADE, see table e-2, doi:10.5061/ dryad.6djh9w0zb). In the included studies, headache recurrence is consistently defined based on a previous definition as the return or worsening of headache within 24 or 48 hours after an initial response (instead of an initial pain-free response). In general, headache recurrence occurs several hours after the half-life time point of triptans. Although frovatriptan has demonstrated lower headache recurrence rates compared with most other triptans, probably because of its long half-life time of 26 hours, recurrence rates are not negligible ranging from 11 to 15% at 24-48 hours.[28] Hence, we conclude that headache recurrence is not directly related to triptan plasma levels because we even showed that women have higher total drug exposure than men and both sexes have similar plasma half-life times. The higher headache recurrence in women despite their higher drug exposure may be explained by the longer attack duration related to sex hormonal changes, such as menstrually related migraine attacks or perimenopausal attacks. Previous studies showed that menstrually related migraine attacks have a longer duration, are less responsive to acute therapy, and are more prone to headache recurrence after treatment with triptans compared with migraine attacks occurring outside the menstrual period.[29-31] In addition, major fluctuations in estrogen levels during perimenopausal transition are associated with an increased prevalence of migraine and an increased risk of high frequency headache.[32-34] Although data regarding attack duration and the risk of headache recurrence specifically in perimenopausal women are lacking, we hypothesize that sex hormonal changes during perimenopause may be of influence on these outcomes.

Our study also has some limitations. Important methodological differences were found across clinical trials, including the approach of blinding, type and dose of treatment, follow-

up duration, and the use of headache recurrence after 24 and/or 48 hours as outcome parameter. Based on the χ^2 test of Q, statistical heterogeneity of the effect between studies was observed for headache response after 2 hours and $AUC_{0-\infty}$, so results of these analyses should be interpreted with caution. Although no significant statistical heterogeneity arose from methodological diversity between studies in the other outcome measures, this limitation of our study should be kept in mind when interpreting the results. We chose to pool all triptans because separated meta-analyses per triptan could not be performed. Although triptans roughly have the same mechanism of action, it must be stressed that there are pharmacodynamic and pharmacokinetic differences between triptans. Pharmacodynamic differences between triptans may include variation in lipophilicity, the ability to cross the blood-brain barrier, and differences in 5-$HT_{1B,}$ 5-$HT_{1D,}$ and 5-HT_{1F} receptor affinities.[35] Pharmacokinetic differences between oral triptans are $T_{½}$ differences ranging from 2 to 26 hours (exceptionally long for frovatriptan with 26 hours) and T_{max} ranging from 1 to 4 hours, main excretion route through hepatic drug metabolism (by cytochrome P450 and monoamine oxidase enzymes) except for naratriptan, which is partly metabolized by renal excretion.[12,36-38] We have tried to take these limitations into account by using random-effects models for our analyses. Furthermore, in modern meta-analytical approaches, it is unusual to conduct pooled analyses across few studies. Nevertheless, in some analyses, we chose to pool across only a few studies because limited data were available, and one of our aims was to address that results are currently rarely presented separately for men and women. Although we have performed random-effects meta-analyses, which weight the studies relatively more equally than fixed-effect analyses, most weight was given to one study in pooled analyses on adverse event rates and headache recurrence rates. However, it is reassuring that also smaller, medium-sized clinical trials presenting results on these outcomes point in the same direction as the larger studies. The included studies on sex differences in pharmacokinetic outcomes of triptans are performed in healthy volunteers. However, migraine attacks may be of influence on drug absorption because of delayed gastric emptying and thereby may cause additional variability in pharmacokinetic parameters.[39] Gender differences could not be specifically addressed because corresponding information was not presented in the included studies. Finally, publication bias might be an issue in the reporting of clinical trials because negative findings are less likely to get published. However, it concerned mainly large clinical trials investigating the efficacy and tolerability of triptans, which are less likely to be unpublished. Indeed, visual inspection of funnel plots was unsuspected for publication bias; however, it cannot be excluded. Tests for funnel plot asymmetry were not used because test power is usually too low to distinguish chance from real asymmetry when less than 10 studies are included in the meta-analysis.

We encourage physicians treating patients with migraine to be aware that their female migraine patients will likely report more adverse events after the intake of triptans and more headache recurrences compared with male migraine patients. Physicians should be aware that dose reduction to reduce adverse events seems undesirable because this might further increase the risk for headache recurrence in women and might also affect initial efficacy. Instead, menstrually related attacks and nonmenstrually related attacks should be assessed separately. We also want to underline the importance of prescribing preventive treatments in migraine patients to diminish frequency, duration, and severity of attacks. As we hypothesize that the longer attack duration in women relates to sex hormonal changes, there is an urgent need for clear evidence whether preventive hormonal treatments are effective (ClinicalTrials.gov NCT04007874). In addition, dedicated studies on gender-related differences in migraine are needed. Finally, we would like to call on headache researchers to present data by sex and, if information is collected, also by gender when performing clinical trials on the efficacy and tolerability of acute and preventive migraine treatments. So far, this has only occasionally been performed for today's important clinical trials on migraine prevention with monoclonal antibodies acting on calcitonin gene-related peptide or on its receptor.

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Table e-1. Description of individual characteristics of included studies.

	Name	Year	Study design	Intervention with separate results	Sample size (males/females)	Population	Follow-up duration
Studies on clinical response outcomes	Cady et al.[40]	1998	Uncontrolled open-label study	Zolmitriptan 5 mg	n=288 / n=1769	Migraine without aura + with aura	One attack - >12 months
	Tuchman et al.[41]	1999	Non-randomized open-label cross-over study	Zolmitriptan 2.5 mg and zolmitriptan 5 mg	n=347 / n=2152 n=347 / n=2152	Migraine without aura + with aura	6 months
	Edmeads et al.[42]	1997	Randomized double-blind placebo-controlled studies and uncontrolled open-label studies	Zolmitriptan 2.5 mg Zolmitriptan 5 mg Placebo	n=63 / n=498 n=158 / n=854 n=62 / n=339	Migraine without aura + with aura	Single attack or multiple attacks
	Schoenen et al.[43]	1997	Randomized double-blind placebo-controlled studies	Zolmitriptan 2.5 mg	n= 64 / n=425	Migraine without aura + with aura	Single attack
	Pascual et al.[44]	2001	Uncontrolled open-label study	Almotriptan 12.5 mg	n=93 / n=669	Migraine without aura + with aura	One attack - >12 months
	Ho et al.[13]	2009	Randomized double-blind placebo-controlled studies	Rizatriptan 10 mg Placebo	n=237 / n=1538 n=154 / n=939	Migraine without aura + with aura	Treatment of single attack
	Ashford et al.[45]	1998	Randomized double-blind placebo-controlled studies	Sumatriptan nasal spray 10 mg Sumatriptan nasal spray 20 mg Placebo	n=107 / n=709* n=140 / n=871* n=82 / n=486*	Migraine without aura + with aura	Single attack or three attacks
	Dodick et al.[46]	2008	Randomized double-blind placebo-controlled studies	Eletriptan 40 mg, eletriptan 80 mg, sumatriptan 100 mg and placebo	n=591 / n=3714	Migraine without aura + with aura	Single attack
	Franconi et al.[47]	2014	Randomized double-blind controlled cross-over studies	Frovatriptan 2.5 mg Comparator: rizatriptan 10 mg, zolmitriptan 2.5 mg and almotriptan 12.5 mg	n=66 / n=280 n=66 / n=280	Migraine without aura + with aura	6 months
	Sheftell et al.[48]	2010	Prospective observational study	Triptans in general	n=33 / n=326	Migraine without aura + with aura	6 months

*Represents sample sizes for the evaluation of frequency of adverse events as outcome measurement. The headache response 2 hours after treatment was calculated based on smaller sample sizes.

	Name	Year	Study design	Intervention with separate results	Sample size (males/females)	Population	Follow-up duration
Studies on pharmacokinetic outcomes	Peck et al.[25]	1998	Randomized double-blind placebo-controlled cross-over study	Zolmitriptan 5 mg Zolmitriptan 10 mg Zolmitriptan 15 mg	n=12 / n=12 n=12 / n=12 n=12 / n=12	Healthy adult + elderly volunteers	-
	Smith et al.[14]	1998	Randomized double-blind placebo-controlled cross-over study	Zolmitriptan 5 mg Zolmitriptan 10 mg Zolmitriptan 20 mg	n=16 / n=17 n=16 / n=17 n=16 / n=17	Healthy adult volunteers	-
	Seaber et al.[21]	1997	Randomized open-label cross-over study	Zolmitriptan 10 mg	n=6 / n=6	Healthy adult volunteers	-
	Seaber et al.[22]	1998	Randomized open-label cross-over study	Zolmitriptan 2.5 mg Zolmitriptan 5 mg	n=10 / n=10 n=10 / n=10	Healthy adult volunteers	-
	Yates et al.[11]	2002	Uncontrolled open-label study	Zolmitriptan 2.5 mg	n=15 / n=15	Healthy adult Japanese volunteers	-
	Musson et al.[24]	2001	Randomized double-blind placebo-controlled study	Rizatriptan 10 mg	n=8 / n=8	Healthy elderly volunteers	-
	Lee et al.[23]	1999	Randomized open-label cross-over study	Rizatriptan 2.5 mg Rizatriptan 5 mg Rizatriptan 10 mg Rizatriptan 15 mg	n=12 / n=12 n=12 / n=12 n=12 / n=12 n=12 / n=12	Healthy adult volunteers	-
	Goldberg et al.[49]	2000	Randomized double-blind placebo-controlled study	Rizatriptan 10 mg	n=8 / n=8	Healthy adult volunteers	-
	Buchan et al.[12]	2002	Review including results of a randomized open-label cross-over study	Frovatriptan 2.5 mg Frovatriptan 40 mg	n=6 / n=6 n=6 / n=6	Healthy adult volunteers	-

*Represents sample sizes for the evaluation of frequency of adverse events as outcome measurement. The headache response 2 hours after treatment was calculated based on smaller sample sizes.

Table e-2. GRADE assessments for two outcomes: adverse event frequency after the intake of triptans (A) and risk for headache recurrence (B).

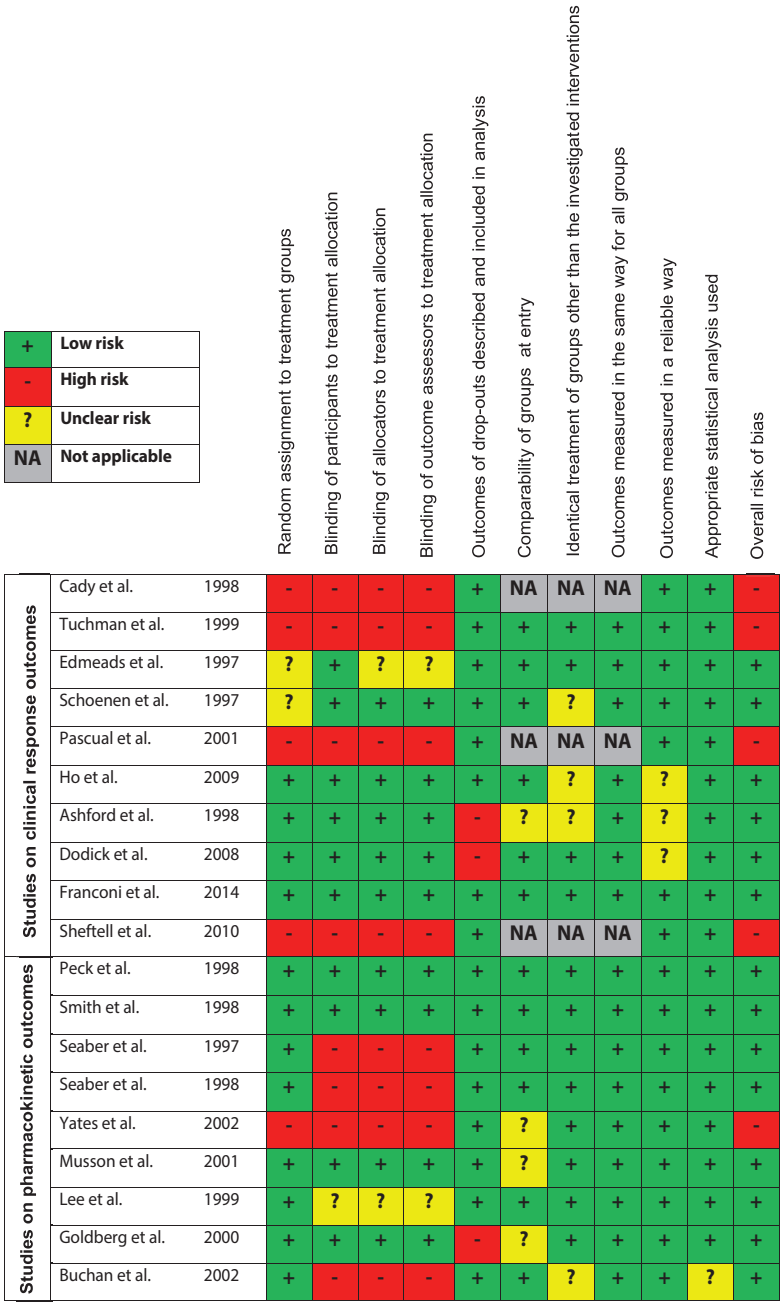
A. GRADE criteria	Rating	Quality of evidence (high, moderate, low or very low)
Outcome: Adverse event frequency after the intake of triptans		
Study design	RCTs and non-RCTs – high score	
Risk of Bias	Serious (-1)	
Inconsistency	No	Moderate
Indirectness	No	
Imprecision	No	
Publication Bias	Undetected	

B. GRADE criteria	Rating	Quality of evidence (high, moderate, low or very low)
Outcome: Risk of headache recurrence		
Study design	RCTs and non-RCTs – high score	
Risk of Bias	No	
Inconsistency	No	Moderate
Indirectness	No	
Imprecision	Serious (-1)	
Publication Bias	Undetected	

Figure e-1. Search strategy for PubMed.

(("rizatriptan"[Supplementary Concept] OR "rizatriptan"[tw] OR rizatriptan*[tw] OR "MK 0462"[tw] OR "MK-0462"[tw] OR "MK-462"[tw] OR "MK 462"[tw] OR "maxalt"[tw] OR "almotriptan"[Supplementary Concept] OR "almotriptan"[tw] OR almotriptan*[tw] OR "Almogran"[tw] OR "eletriptan"[Supplementary Concept] OR "eletriptan"[tw] OR eletriptan*[tw] OR "UK 166,044"[tw] OR "UK-166044"[tw] OR "UK 166044"[tw] OR "UK-166,044"[tw] OR "Relpax"[tw] OR "UK-116044-04"[tw] OR "UK-116,044-04"[tw] OR "Sumatriptan"[Mesh] OR "sumatriptan"[tw] OR sumatriptan*[tw] OR "GR-43175"[tw] OR "GR 43175"[tw] OR "GR43175"[tw] OR "Imigran"[tw] OR "sumatriptan-naproxen"[Supplementary Concept] OR "zolmitriptan"[Supplementary Concept] OR "zolmitriptan"[tw] OR zolmitriptan*[tw] OR "Zomig"[tw] OR "311C90"[tw] OR "frovatriptan"[Supplementary Concept] OR "frovatriptan"[tw] OR frovatriptan*[tw] OR "VML-251"[tw] OR "VML251"[tw] OR "SB 209509"[tw] OR "fromirex"[tw] OR "naratriptan"[Supplementary Concept] OR "naratriptan"[tw] OR naratriptan*[tw] OR "GR 85548A"[tw] OR "Naramig"[tw] OR "triptans"[tw] OR "triptan"[tw] OR triptan*[tw] OR "Tryptamines"[Mesh:NoExp]) AND (("female"[tiab] OR "females"[tiab] OR "woman"[tiab] OR "women"[tiab]) AND ("male"[tiab] OR "males"[tiab] OR "man"[tiab] OR "men"[tiab])) OR "Sex Characteristics"[mesh] OR "Sex"[mesh] OR "Sex Factors"[mesh] OR "Sex Ratio"[mesh] OR gender*[tw] OR sex differenc*[tw] OR "sex"[ti] OR ("Female"[mesh] AND "Male"[mesh] AND ("sex"[tw] OR gender*[tw]))) AND ("Clinical Trial"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR random*[tiab] OR double blind*[tiab] OR "RCT"[tiab] OR "trial"[tiab] OR "systematic"[sb] OR "Meta-Analysis"[Publication Type] OR "Meta-Analysis"[ti] OR "Metaanalysis"[ti] OR Meta-Analy*[ti] OR Metaanaly*[ti] OR placebo*[ti]) AND ("Migraine Disorders"[mesh] OR "migraine"[tw] OR migrain*[tw] OR anti-migrain*[tw] OR antimigrain*[tw]))

Figure e-2. Risk of bias assessments based on JBI Critical Appraisal Checklist for Randomized Controlled/ Pseudo-randomized Trials.



CHAPTER 3

Sex differences in prevalence of migraine trigger factors: A cross-sectional study

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Abstract

Aim To examine the effect of sex on migraine trigger factors.

Methods Prevalence of 11 frequently reported trigger factors was determined in a cross-sectional study among migraine patients from a validated migraine database (n = 5725 females and n = 1061 males). Female-to-male odds ratios were calculated for each trigger, using a logistic regression model with attack frequency and migraine subtype (with or without aura) as covariates. Additionally, the effect of sex on total number of triggers per individual was determined.

Results The top three most reported triggers in women were menstruation (78%), stress (77%), and bright light (69%). Men reported stress (69%), bright light (63%), and sleep deprivation (60%) most frequently as provoking factors. The following triggers were more often reported by women than men: Bright light (odds ratio 1.29 [95% CI 1.12-1.48]; $p = 0.003$), stress (1.47 [1.27-1.69]; $p < 0.001$), skipping a meal (1.24 [1.09-1.42]; $p = 0.015$), sleep deprivation (1.37 [1.20-1.57]; $p < 0.001$), high altitudes (1.70 [1.40-2.09]; $p < 0.001$), and weather changes (1.35 [1.18-1.55]; $p < 0.001$). Women reported more triggers than men, even when menstruation was disregarded (mean ± SD: 4.6 ± 2.3 and 4.3 ± 2.3; $p < 0.001$).

Conclusion Women report migraine trigger factors to be provocative of their attacks more frequently than men, which may be related to a lower migraine threshold due to sex hormonal changes.

Key words: menstruation, stress, light, sleep, primary headache

Introduction

Migraine is a multifactorial brain disorder characterised by recurring attacks of severe headaches and neurological features. How attacks exactly are initiated is unknown. Migraine susceptibility seems to be determined by a complex interaction between internal threshold modulating factors and external modifiable factors. Internal threshold modulating components mainly consist of genetic factors and sex hormonal conditions. Differences in sex hormonal conditions may explain why migraine prevalence is three times higher in fertile women than in men. During the fertile period, sex hormonal fluctuations preceding menstruation lower the threshold and thus increase susceptibility to a migraine attack.[1-4] External modifiable factors may trigger an attack, especially when the threshold is already low; for example, during menstruation. Many patients and physicians are convinced that attacks are provoked by external triggers such as certain food items, skipping a meal, alcohol, stress, and weather changes.[5-8] In previous migraine trigger-related research, remarkably little attention has been paid to sex differences, which is surprising given the large influence of sex on migraine prevalence. The aim of this study was to investigate sex differences in trigger factors in a large, well-defined cohort of migraine patients. Although behavioural, social, environmental and cultural factors are expected to be of influence as well, we chose to use the term "sex" to comprehensibly describe differences between men and women in this study.

Methods

Study design and population

This study is a cross-sectional, web-based questionnaire study among female and male migraine patients. This study was conducted as part of the Leiden University MIgraine Neuro-Analysis (LUMINA) project, a validated migraine population.[9] Participants in the LUMINA project are Dutch adults suffering from migraine with or without aura based on the International Classification of Headache Disorders (ICHD-3) criteria.[10] An elaborate description of LUMINA participants and procedures is found as supplemental material. The study was approved by the medical ethics committee of Leiden University Medical Center (METC number P12.201). All participants provided written informed consent. Recruitment for the LUMINA study population is still ongoing, but for the current study we included participants recruited between 2008 and 2018.

LUMINA questionnaire

All participants completed an extended online questionnaire (accessible via www.lumc.nl/hoofdpijn) that incorporated 11 items on trigger factors. The prevalence of frequently reported trigger factors was assessed by the question: Which of the following factors can provoke migraine attacks? 1. Bright (sun)light. 2. Stress. 3. Physical exercise and/or sexual activity. 4. Mild head trauma. 5. Skipping a meal. 6. Certain food or non-alcoholic beverages. 7. Alcoholic beverages. 8. Sleep deprivation. 9. High altitudes (for instance in the mountains). 10. Weather changes. Answer possibilities were No/Yes/Don't know. Participants were motivated to answer positively when a certain factor inconsistently provokes severe headaches. Additionally, women were asked to indicate the relation between migraine attacks and menstruation, defined as attacks occurring on −2 days of the onset of menstruation to +2 days from the end of menstruation, using the following answer possibilities: 1.There is no association between my headache and the menstrual period; 2. My headache exclusively occurs related to the menstrual period and at no other times of the cycle; 3. My headache occurs related to the menstrual period and additionally at other times of the cycle, or 4. Not applicable. Data on current use of contraceptives was not collected.

Data analysis and statistics

Independent-samples t-tests and Chi-square tests were used to compare baseline characteristics between female and male migraine patients. Logistic regression models were conducted to calculate female-to-male odds ratios for each trigger factor. Migraine attack frequency was included as covariate, as we expect this to influence the recall of trigger factors. Migraine subtype (migraine without aura (MO) or migraine with aura (MA)) was also included as covariate, as knowledge regarding its influence on the role of trigger factors is insufficient. *P*-values were adjusted for multiple testing with a Bonferroni correction. Additionally, a linear regression model was conducted to compare the total number of trigger factors between females and males, including migraine attack frequency and migraine subtype as covariates. Menstruation as trigger factor was disregarded in these analyses. The frequency of "don't know" answers to the questions regarding migraine trigger factors was compared between men and women and appeared to be similar.

Results

Participants

A total of 6786 patients completed the LUMINA questionnaire. Baseline characteristics of female (n = 5725) and male (n = 1061) participants are shown in Table 1. Women were younger (mean age in years ± SD: 41.9 ± 12.1 vs. 45.7 ± 13.1, p < 0.001), with a lower body mass index (BMI) (24.5 ± 6.4 vs 25.8 ± 13.3, p < 0.001), and a higher percentage of migraine without aura diagnoses (64.5% vs 57.2%, p < 0.001). Fourteen percent of the female population was 55 years of age or older and likely postmenopausal (n = 825). Men more often experienced low frequency migraine (1-6 attacks/year) and very high frequency migraine (> 54 attacks/year) compared to women (18.7% vs 13.7% and 23.0% vs 16.6% respectively). Mean number of migraine days per month and mean number of headache days per month did not differ between men and women.

Table 1. Baseline characteristics of the study population.

	Female (n = 5725)	Male (n = 1061)
Age in years, mean ± SD	41.9 ± 12.1	45.7 ± 13.1
Age range in years	18.0 : 82.7	18.0 : 83.6
BMI, mean ± SD	24.5 ± 6.4	25.8 ± 13.3
Migraine without aura, n (%)	3694 (64.5)	607 (57.2)
Migraine attack frequency per year, n (%)		
1-2	167 (2.9)	47 (4.4)
3-6	617 (10.8)	152 (14.3)
7-12	1395 (24.4)	216 (20.4)
13-54	2593 (45.3)	402 (37.9)
>54	951 (16.6)	244 (23.0)
Migraine days per month, mean ± SD	7.6 ± 8.8	7.6 ± 9.6
Other headache days per month, mean ± SD	7.3 ± 12.2	7.0 ± 12.3

Primary analysis

The top three most reported trigger factors in women were menstruation (78.1%), stress (76.7%), and exposure to bright light (68.5%) (Table 2 and Figure 1). The large majority of women with a menstrual cycle stated their attacks to be related to their menstrual cycle. Only 4.7% of women reported attacks to be exclusively related to menstruation (pure menstrual migraine)[10], most (73.4%) indicated that besides the menstruation period, attacks also occur at other time periods in the cycle (menstrually related migraine).[10] Men reported stress (69.2%), exposure to bright light (63.2%), and sleep deprivation (60.3%) most frequently as migraine provoking factors (Table 2 and Figure 1). The following trigger

factors were more often reported by women than men after correction for attack frequency and migraine subtype: Exposure to bright light (odds ratio 1.29 [95% CI 1.12-1.48]; p = 0.003), stress (1.47 [1.27-1.69]; p < 0.001), skipping a meal (1.24 [1.09-1.42]; p = 0.015), sleep deprivation (1.37 [1.20-1.57]; p < 0.001), high altitudes (1.70 [1.40-2.09]; p < 0.001) and weather changes (1.35 [1.18-1.55]; p < 0.001) (Table 2 and Figure 1). Prevalence of physical exercise/sexual activity, mild head trauma, certain food/non-alcoholic beverages, and alcoholic beverages as migraine trigger factors did not differ significantly between men and women (Table 2 and Figure 1).

Table 2. Prevalence of migraine trigger factors separately for both sexes and female-to-male odds ratios for all triggers.

	Percentage(%)			
	Female (n = 5725)	Male (n = 1061)	Odds ratio 95% CI	Adjusted p-value
Menstruation	78.1	-	-	-
Stress	76.7	69.2	1.47 (1.27-1.69)	< 0.001
Bright (sun)light	68.5	63.2	1.29 (1.12-1.48)	0.003
Sleep deprivation	67.7	60.3	1.37 (1.20-1.57)	< 0.001
Skipping meals	47.9	42.4	1.24 (1.09-1.42)	0.015
Alcoholic beverages	45.0	45.5	0.96 (0.84-1.10)	1
Physical exercise/sexual activity	41.7	45.8	0.84 (0.74-0.96)	0.114
Weather changes	45.9	38.7	1.35 (1.18-1.55)	< 0.001
Certain food/non-alcoholic beverages	28.6	31.9	0.86 (0.75-1.00)	0.424
Mild head trauma	24.5	21.9	1.15 (0.98-1.35)	0.794
High altitudes	18.0	11.5	1.70 (1.40-2.09)	< 0.001

Note: The included number of participants per trigger slightly differs from the numbers mentioned at the top of the table.

Additional analyses

Women reported a larger total number of migraine trigger factors than men (mean ± SD: 4.6 ± 2.3 and 4.3 ± 2.3 respectively), with most women reporting five trigger factors (16.9%) compared to four trigger factors in men (17.2%). A significant regression equation was found after correcting for attack frequency and migraine subtype (see Table 3, p < 0.001). Female sex appeared to be associated with a higher total number of reported trigger factors compared to men, even when menstruation was disregarded in the analysis (β = 0.32, p < 0.001). The number of triggers was positively associated with migraine attack frequency (β = 0.42, p < 0.001). On the contrary, migraine subtype (with or without aura) appeared to have no effect on the total number of reported triggers (β = 0.04, p = 0.508) (Table 3).

Most postmenopausal women reported four or five trigger factors (13.7% and 13.9% respectively, mean ± SD: 4.4 ± 2.5), which appeared to be comparable to the total number of trigger factors reported by men after correcting for attack frequency and migraine subtype (p = 0.371).

Figure 1. Prevalence of migraine trigger factors in females and males.

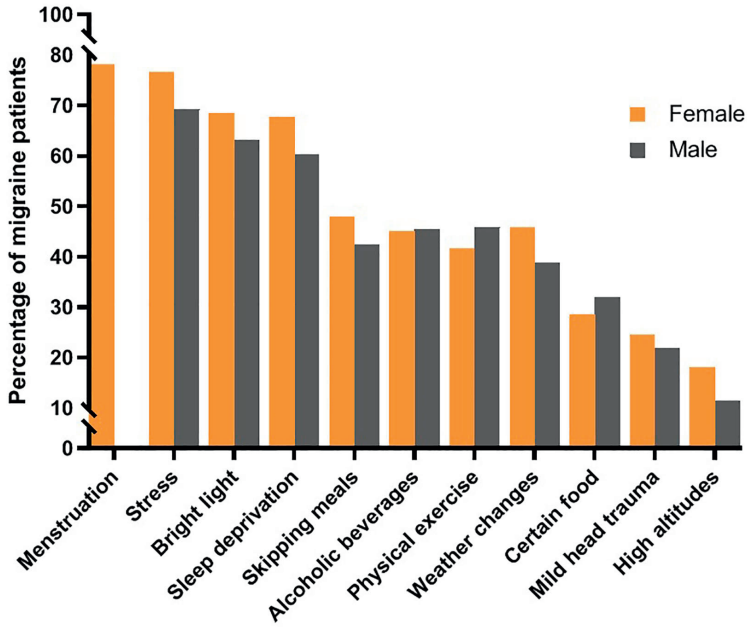

Table 3. Linear model of predictors of the number of reported trigger factors.

	Estimate (β)	SE	t-value	p-value
Constant	2.69	0.141	19.03	< 0.001
Sex (female)	0.32	0.076	4.30	< 0.001
Migraine attack frequency	0.42	0.026	16.00	< 0.001
Migraine subtype (MO/MA)	0.04	0.057	0.66	0.508

Discussion

Menstruation, stress and exposure to bright light are the most reported migraine trigger factors in our large validated migraine population. Women have a higher self-reported prevalence of migraine trigger factors than men, especially concerning skipping a meal, sleep deprivation, stress, exposure to bright light, weather changes and high altitudes.

The susceptibility to migraine attacks is suggested to be determined by natural fluctuations in neuronal excitability in the brain. The brain may be much more susceptible to triggers at the peak of these neuronal excitability fluctuations. We hypothesise that migraine susceptibility is determined by a complex interaction between internal threshold modulating factors and external modifiable factors. These internal threshold components are partly stable, such as genetic predisposition factors, and partly fluctuating, such as sex hormonal conditions.[1,11,12] When internal threshold factors decrease the threshold at a certain point in time, susceptibility to an attack will be high. At this point, external trigger factors may provoke an attack whereas at other time points, when the internal threshold is high and susceptibility to an attack is low, these external factors are not able to provoke a migraine attack.

We also hypothesise that sex hormonal differences between males and females may contribute to a different pattern of fluctuations in neuronal brain excitability and the internal threshold, and therefore, to an increased potential of external trigger factors to provoke migraine in women. Our hypothesis is supported by the finding that the total number of trigger factors reported by postmenopausal women with stabilised sex hormones was comparable to the results in men. Additionally, previous clinical and experimental pain research demonstrated a lower pain threshold and greater pain sensitivity in women than in men. Although the exact pathophysiological underlying mechanism is unknown, the influence of sex hormones on nociceptive processing is suggested to be of great importance.[13,14]

An alternative explanation for our findings may be related to behavioural, social and cultural differences between men and women in reporting health-related outcomes. Epidemiological pain research has shown that women are more likely than men to report symptoms of pain, such as headaches, musculoskeletal pain and abdominal pain.[15] Women also tend to report adverse drug reactions more frequently than men.[16,17] However, the reported number of migraine days and headache days per month was comparable in men and women in our study, suggesting that in our study there were no sex differences in reporting pain-related outcomes.

The most important strength of the current study includes the large cohort of well-defined patients suffering from migraine with and without aura. In contrast to previous studies, our study is sufficiently powered to investigate sex differences regarding the prevalence of trigger factors. A possible limitation of the current study is the self-reported nature, which makes it susceptible to recall bias. Furthermore, frequently reported trigger factors were selected for investigation in this study, but more factors are suggested as potential migraine triggers, such as odours, noise and smoking.[18] However, trigger-related research is complicated by overlap of trigger factors and premonitory symptoms. Many putative trigger factors might in fact be part of the premonitory symptom phase, reflecting an attack that has already started rather than true inducers of migraine attacks. Thus, migraine patients may perceive factors such as odours, noise, and bright sunlight more intensely during the premonitory phase as a result of an enhanced neuronal susceptibility.[5] Therefore, we selected mostly trigger factors that are not also among the most frequently reported premonitory symptoms.[19,20] Nevertheless, the uncertainty associated with overlapping trigger factors and premonitory symptoms should be born in mind when interpreting results on perceived triggers, especially regarding bright light, stress, sleep deprivation and skipping meals. Lastly, the temporal window used to consider a migraine attack related to the peri-menstrual period was expanded compared to the current ICHD-3 criteria[10], which may have affected the prevalence of women reporting menstruation as trigger factor. The lack of uniform criteria for the definition of the peri-menstrual period in the past has demonstrated prevalence differences.[21] Additionally, accuracy of self-reported menstrual migraine diagnoses has shown to be poor in female migraine patients.[22] However, accurate menstrual migraine diagnoses are difficult to obtain even when prospective diaries are collected, since the current ICHD-3 diagnostic criteria for menstrual migraine have shown to reach maximum sensitivity for three menstrual cycles, although specificity increased with more cycles of data collection.[23]

To further study the role of trigger factors in male and female migraine patients, a prospective electronic headache-trigger diary may be applied to screen for a close temporal relationship between the suspected trigger and attack onset. Electronic registration of objective measurements, such as weather changes and sleeping patterns, in combination with headache diaries would increase the reliability of trigger research even further. Additionally, it would be interesting to investigate suspected external trigger factors at different time points of the menstrual cycle in order to assess the influence of menstrual cycle status on the triggering effect. Two pilot questionnaire studies were performed at our Headache clinic to assess patients' willingness to participate in future detailed trigger-related research. The first group comprised 53 male and female migraine

patients who were asked about multiple trigger factors and willingness to participate in a prospective headache-trigger diary study. The second group included 48 female migraine patients who were asked about the influence of sex-hormonal changes on migraine and their willingness to participate in a diary study. In the first group, 92% of male and female migraine patients indicated that more research needs to be performed addressing trigger factors in migraine and 64% were willing to participate in a headache-trigger diary study. In the second group, 85% of women stated that the role of sex hormones in migraine should be further investigated and 77% of patients with sex-hormonal related migraine were willing to participate in a diary study. These results are promising when it comes to future inclusion of participants in detailed and prospective trigger-related studies.

Clinical implications

- Women report more migraine trigger factors than men.
- Menstruation, stress and exposure to bright light are the most reported migraine trigger factors.

Ethics approval: The study was approved by the medical ethics committee of Leiden University Medical Center (METC number P12.201). All subjects provided written informed consent.

Supplementary data availability: Data not published within the article will be shared by request from any qualified investigator.

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Online supplementary information

LUMINA Background information

Dutch migraine patients aged 18-80 years were recruited via nationwide public announcement, advertising in lay press and our research website (www.lumc.nl/hoofdpijn). They were considered eligible after a two-step inclusion process using validated questionnaires via the dedicated Leiden University MIgraine Neuro-Analysis (LUMINA) website. Additionally, patients attending our outpatient headache clinic were invited to participate by a letter. Patients were first asked to fill out a validated web-based screening questionnaire with a sensitivity of 0.93 and specificity of 0.36.[1] Patients who fulfilled the screening criteria, were sent a validated web-based extended migraine questionnaire[2], based on the International Classification of Headache Disorders criteria (previously ICHD-2, now ICHD-3 version) criteria.[3] The specificity of the second questionnaire was 0.95 and sensitivity was 0.45.[2] This questionnaire is accessible for patients via our research website and is described in English in detail by van Oosterhout et al. 2011.[2] We consider the cohort a well-defined web-based cohort. Four percent of subjects were included from our headache outpatient clinic and 87% of the participants were previously diagnosed with migraine by a physician. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, aura and headache characteristics, acute and prophylactic headache medication use, and allodynia. Participants unable to use the web-based questionnaires due to lack of the needed internet skills were allowed to fill out the questionnaires on paper.

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PART II

Clinical female-specific characteristics of migraine

CHAPTER 6

Jealousy in women with migraine: A cross- sectional case-control study

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Abstract

Background Estrogen influences susceptibility to migraine attacks and it has been suggested to affect jealousy in romantic relationships in women. Therefore, we hypothesized that migraine women may be more jealous.

Methods Jealousy levels and hormonal status were determined based on a cross-sectional, web-based, questionnaire study among female migraine patients and controls. A random sample of participants was selected from a validated migraine database. Participants with a serious and intimate monogamous relationship were included (n = 498) and divided into the following subgroups: menstrual migraine (n = 167), non-menstrual migraine (n = 103), postmenopausal migraine (n = 117), and premenopausal (n = 57) and postmenopausal (n = 54) controls. The primary outcome was the difference in mean jealousy levels between patients with menstrual migraine, non-menstrual migraine and premenopausal controls. Results were analyzed with a generalized linear model adjusting for age, relationship duration and hormonal status (including oral contraceptive use). Additionally, the difference in jealousy levels between postmenopausal migraine patients and controls was assessed. Previous research was replicated by evaluating the effect of combined oral contraceptives on jealousy.

Results Jealousy levels were higher in menstrual migraine patients compared to controls (mean difference ± SE: 3.87 ± 1.09, $p = 0.001$), and non-menstrual migraine patients compared to controls (4.98 ± 1.18, $p < 0.001$). No difference in jealousy was found between postmenopausal migraine patients and controls (-0.32 ± 1.24, $p = 0.798$). Women using combined oral contraceptives were more jealous compared to non-users with a regular menstrual cycle (2.32 ± 1.03, $p = 0.025$).

Conclusion Young women with migraine are more jealous within a romantic partnership.

Keywords: migraine, jealousy, estrogen

Background

Sex hormones have a major influence on migraine, appearing from a three times higher migraine prevalence in premenopausal women compared to men, an increase in attack frequency during menopausal transition, and a postmenopausal decrease of symptoms.[1-3] Furthermore, the fluctuation of estrogen prior to menstruation is evidently linked to an increased susceptibility to an upcoming attack.[4] Two subtypes of migraine with menstruation-associated attacks exist: pure menstrual migraine (PMM) and menstrually-related migraine (MRM). In MRM, attacks occur additionally at other times of the cycle. For research purposes, PMM and MRM are often taken together and defined as menstrual migraine (MM).[5] Although the exact pathophysiological underlying mechanism remains unclear, previous research has suggested that fluctuations in estrogen levels, possibly the rate of decrease in estrogen, may affect the susceptibility to migraine attacks in women and/or higher estrogen levels may be implicated in both sexes.[2,6-9]

Problems within a romantic relationship, such as jealousy, divorce, and bereavement after the suicide of a partner potentially have a large impact on quality of life.[10,11] Knowledge on potential associations between relationship problems and disabling chronic diseases, such as migraine, may increase our understanding, reduce stigma, and improve disease outcomes. Relationship jealousy can be defined as thoughts, emotions, or behaviors that occur as a result of the perceived threat of losing a partner to an actual or imagined rival.[12] In the fertile phase, when estrogen levels are high, women tend to report higher jealousy levels compared to other times of the menstrual cycle.[13] Furthermore, jealousy seems to be affected by the use of combined oral contraceptives. Especially using formulations with higher doses of ethinyl estradiol are associated with significantly higher jealousy scores.[13-15] These findings indicate that estrogen plays a role in jealousy within a romantic relationship, but the exact underlying mechanism is unknown.

That biological factors may affect mental health has been illustrated by previous research concluding that alterations in prolactin and thyroid hormone levels are associated with suicide attempts in psychiatric patients.[16]

We hypothesized that women with migraine, especially those fulfilling the criteria of MM, would have higher jealousy levels compared to women with non-menstrual migraine (non-MM) and premenopausal controls due to a corresponding provoking effect of estrogen in migraine and jealousy. Secondarily, we hypothesized that postmenopausal

migraineurs and controls report low and similar jealousy levels due to stabilization of sex hormones.[3,17] Lastly, we investigated the effect of using combined oral contraceptives on jealousy, aiming to replicate previous results on this topic.

Methods

Study Design

This study is a cross-sectional, web-based, questionnaire study among female migraine patients and healthy controls, performed in November and December 2018.

Participants

The Leiden University Medical Center MIgraine Neuro Analysis (LUMINA) cohort was used to select women who met the ICHD-3 criteria for migraine and healthy controls.[5] An elaborate description of LUMINA participants and procedures is found in a previous publication and in additional file 1.[18] The study was approved by the medical ethics committee of Leiden University Medical Center. All subjects provided written informed consent prior to the study. A random selection of n = 1024 female migraine patients and controls was made from the LUMINA cohort for this present study.

As inclusion criterium participants were required to have a serious and intimate monogamous relationship, assuming that contributions are equally divided among the partners and both partners have a concern for the welfare of the other, and will therefore respond to each other's needs.[19] Pregnant and breastfeeding women were excluded. Additionally, women with a permanent primary amenorrhea, and therefore lifelong absence of menses, were excluded. Participants received a web-based questionnaire consisting of questions concerning relationship duration, jealousy feelings and thoughts, menstrual cycle status and exogenous sex hormone use. Jealousy scores were determined using the validated Buunks Jealousy scale (Cronbach's alpha = 0.843).[12] This questionnaire consists of five statements for each of the three sub-types of jealousy, i.e. reactive jealousy (a negative response to the emotional or sexual involvement of the partner with someone else), preventive jealousy (efforts to prevent intimate contact of the partner with someone else) and anxious jealousy (obsessive anxiety and worrying about the possibility of infidelity of the partner). A 5-point Likert scale was used to rate how strongly the participants agreed with the statements. Premenopausal migraine patients were categorized as MM or non-MM according to the ICHD-3 criteria.[5]

Covariates

The covariates age, relationship duration and hormonal status were chosen a-priori based on previous studies. Relationship duration was categorized as shorter or longer than 1 year. Although the effect of relationship duration on jealousy levels is inconsistent in previous studies, this covariate was reasoned to be important, and therefore, was included in this study.[20,21] Hormonal status was defined as the use of combined oral contraceptives (COC), use of other hormonal contraceptives or no use of hormonal contraceptives (i.e. naturally menstruating). Other hormonal contraceptives included desogestrel-only pills, levonorgestrel intrauterine devices, etonogestrel subcutaneous implants, medroxyprogesterone injections and an ethinylestradiol/etonogestrel ring. The naturally menstruating group consisted of women with a regular menstrual cycle (i.e. duration of 21 to 35 days) or irregular menstrual cycle (i.e. shorter than 21 days, longer than 35 days or irregular). The use of hormonal contraceptives has been shown to increase jealousy levels and was an important covariate to include in our analyses.[13,14]

Statistical analyses

One-way ANOVA or Chi-square tests were used to compare the characteristics between the different groups. For our primary analysis we performed a generalized linear model to assess the mean difference between the total self-reported jealousy scores of MM, non-MM and premenopausal controls. Age, relationship duration and hormonal status were included as covariates. In a secondary analysis, we compared the mean total jealousy levels of postmenopausal migraine patients and controls using a generalized linear model, adjusting for age and relationship duration. The same statistical model was used to compare mean jealousy levels between women using COC and women with a regular menstrual cycle, controlling for age, relationship duration and migraine status. Mean differences in sub-type jealousy levels were analyzed for the premenopausal groups as exploratory analyses. A p-value of < 0.05 was considered statistically significant.

Results

Participants

A total of 1024 patients were invited to participate in this study, of which 498 were eligible and completed the questionnaire (see Figure 1). The characteristics of the premenopausal and postmenopausal study populations are shown in Tables 1 and 2, respectively. The majority of premenopausal migraine patients was classified as MM (62%), of which 38% fulfilled the criteria of migraine with aura. In the non-MM group, 60% of patients had

migraine with aura. The number of migraine days per month was higher in women with MM compared to women with non-MM, with at least one migraine day per week in 38% of the MM group compared to 20% in the non-MM group. In the postmenopausal migraine group, 39% experienced at least one migraine day per week.

Premenopausal controls and MM patients were more likely to have a regular menstrual cycle than to use hormonal contraceptives. Non-MM patients more frequently used combined oral contraceptives or other hormonal contraceptives. Migraine and/or headache was in 38% of MM patients and in 30% of non-MM patients a reason to start using combined oral contraceptives. MM patients mentioned more frequently headache and/or migraine as reason for starting other hormonal contraceptives compared to non-MM patients (respectively 61% and 45%). Furthermore, women with MM were more likely to be irregularly cycling (20%) compared to controls (9%) and non-MM patients (7%).

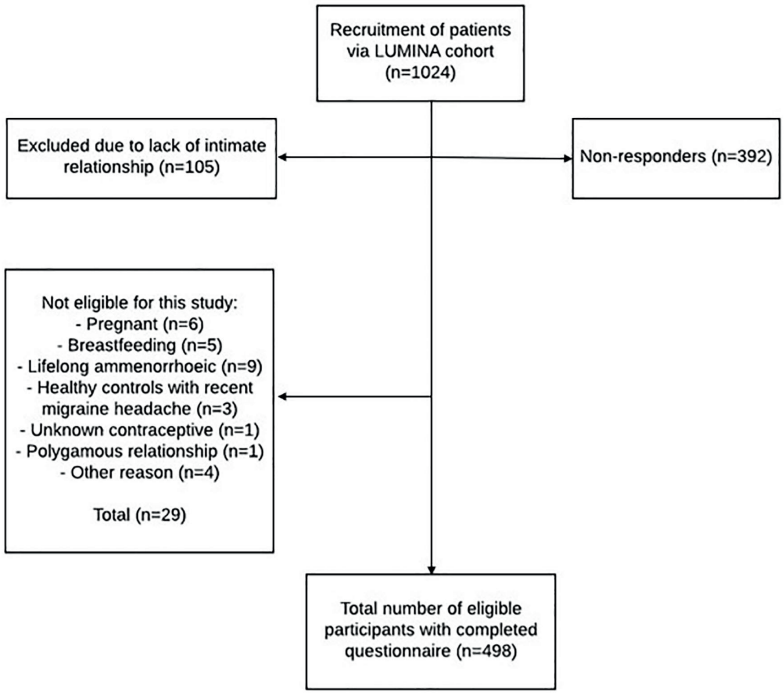
Women using combined oral contraceptives (COC) were younger than women who were regularly cycling (mean 34.9 and 38.5 years, respectively). The percentage of women with a relationship duration of at least 1 year in the COC group was 89%, which was comparable to the group with a regular menstrual cycle (96%). Furthermore, 82% of participants in the COC group had migraine, compared to 79% of the women with a regular menstrual cycle.

Table 1. Characteristics of the premenopausal study population.

	Control (n = 57)	non-MM (n = 103)	MM (n = 167)	p-value
Age, y, mean (SD)	37.2 (9.7)	37.5 (10.3)	38.8 (9.3)	0.401
Relationship duration > 1 year, n (%)	50 (87.7)	89 (86.4)	160 (95.8)	0.015
BMI, mean (SD)	23.1 (3.7)	23.5 (4.1)	23.7 (4.0)	0.594
Menstrual cycle, n (%)	29 (50.9)	31 (30.1)	102 (61.1)	< 0.001
Regular menstrual cycle	24 (42.1)	24 (23.3)	68 (40.7)	
Irregular menstrual cycle	5 (8.8)	7 (6.8)	34 (20.4)	
COC	15 (26.3)	30 (29.1)	37 (22.2)	
Other hormonal contraceptive	13 (22.8)	42 (40.8)	28 (16.8)	
Migraine frequency, n (%)				< 0.001
≤ 1 day/month	-	40 (38.8)	23 (13.8)	
1-4 days/month	-	42 (40.8)	80 (47.9)	
≥ 5 days/month	-	21 (20.4)	64 (38.3)	
Type of migraine, n (%)				< 0.001
Without aura	-	41 (39.8)	103 (61.7)	
With aura	-	62 (60.2)	64 (38.3)	

Non-MM = non-menstrual migraine, MM = menstrual migraine, COC = combined oral contraceptive. A relationship is defined as a serious and intimate monogamous relationship. A regular menstrual cycle is defined as a menstrual cycle duration of 21 to 35 days. Irregular menstrual cycle duration is defined as shorter than 21 days, longer than 35 days or an irregular duration.

Figure 1. Flow diagram of recruitment of participants.



Primary analysis

There was a significant difference in mean total self-reported jealousy levels between MM, non-MM and premenopausal control groups, $X^2(2) = 18.05$, $p < 0.001$. After adjusting for age, relationship duration and hormonal status, the difference between groups remained statistically significant, $X^2(2) = 18.67$, $p < 0.001$. A pairwise comparison with Bonferroni correction revealed that the mean jealousy levels were higher in patients with MM compared to controls (mean difference ± SE: 3.87 ± 1.09, $p = 0.001$), and in non-MM patients compared to controls (4.98 ± 1.18, $p < 0.001$). There was no difference in jealousy levels between the MM and non-MM group (-1.11 ± 0.93, $p = 0.705$) (see Figure 2). Age was negatively correlated with jealousy levels, resulting in a decline of 0.49 points per 5 years, $X^2(1) = 5.1$, $p = 0.024$. The homogeneity of variance, tested with a Levene's test of equality of error variances, was violated in this primary analysis ($F(2,324) = 8.94$, $p < 0.001$). However, using a robust model did not alter the outcome, therefore no adjustments were made to correct for this violation.

Table 2. Characteristics of the postmenopausal study population.

	Postmenopausal control (n = 54)	Postmenopausal migraine (n = 117)	p-value
Age, y, mean (SD)	59.9 (6.2)	58.1 (6.7)	0.093
Relationship duration > 1 year, n (%)	54 (100)	115 (98.3)	0.334
BMI, mean (SD)	24.8 (3.6)	24.6 (4.4)	0.731
Migraine frequency, n (%)			
≤ 1 day/month	-	26 (22.2)	
1-4 days/month	-	45 (38.5)	
≥ 5 days/month	-	46 (39.3)	
Type of migraine, n (%)	-		
Without aura	-	68 (58.1)	
With aura		49 (41.9)	

A relationship is defined as a serious and intimate monogamous relationship.

Secondary analyses

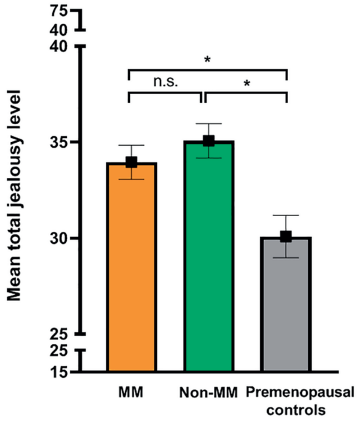
Mean total jealousy levels were similar in postmenopausal migraine patients and controls (mean difference ± SE: -0.41 ± 1.23, p = 0.737). Adjusting for age and relationship duration did not influence the outcome (-0.32 ± 1.24, p = 0.798) (see Figure 3). Women using COC reported higher jealousy levels compared to women with a regular menstrual cycle (2.32 ± 1.03, p = 0.025). After adding age and relationship duration as covariates, this effect became borderline significant (1.86 ± 1.04, p = 0.073). Women with a relationship duration of at least 1 year scored 4.9 points lower compared to women with a relationship duration of less than 1 year, $X^2(1) = 5.6$, p = 0.018. The presence of migraine was associated with an increase of 3.6 points in jealousy levels ($X^2(1) = 8.6$, p = 0.003). However, adding migraine status as covariate did not alter the overall effect of using COC on jealousy levels (1.77 ± 1.02, p = 0.081) (Table 3). Migraine attack frequency was not added as covariate as it did not affect jealousy levels in both, the total group of migraine patients ($X^2(5) = 3.14$, p = 0.678) and the subgroup of premenopausal migraine patients ($X^2(5) = 5.53$, p = 0.355).

Exploratory analyses

Mean differences in the three sub-type jealousy levels (reactive jealousy, preventive jealousy and anxious jealousy) were analyzed for the premenopausal groups as exploratory analyses. A pairwise comparison with Bonferroni correction revealed that both MM and non-MM groups reported higher levels compared to the premenopausal control group for the reactive jealousy sub-type (mean difference ± SE: 1.89 ± 0.64, p = 0.010 and 1.97 ± 0.70, p = 0.014, respectively). Similarly, both MM and non-MM groups reported higher anxious jealousy levels compared to premenopausal controls (1.24 ± 0.49, p = 0.035 and

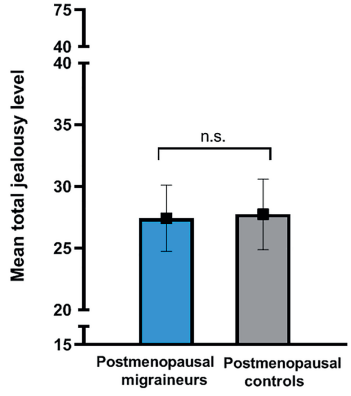
1.83 ± 0.53, p = 0.002, respectively). No statically significant difference was found in mean preventive jealousy levels between premenopausal controls and MM patients (-0.74 ± 0.35, p = 0.104). Non-MM patients reported higher mean preventive jealousy scores compared to premenopausal controls (1.18 ± 0.38, p = 0.005).

Figure 2. Mean of total jealousy levels controlled for age, relationship duration and hormonal status.



Premenopausal women: MM = menstrual migraine; non-MM = non-menstrual migraine; Premenopausal non-migraine controls. Jealousy levels were determined using the validated Buunks Jealousy scale (score between 15 and 75). Depicted levels are mean ± SEM. * = statistically significant difference, n.s. = non-statistically significant difference.

Figure 3. Mean of total jealousy levels controlled for age and relationship duration.



Postmenopausal women: Postmenopausal migraine patients; Postmenopausal non-migraine controls. Jealousy levels were determined using the validated Buunks Jealousy scale (score between 15 and 75). Depicted levels are mean ± SEM. n.s. = non-statistically significant difference.

Table 3. Comparison of jealousy levels between women using COCs and women with a regular menstrual cycle.

	Combined oral contraceptive (n = 82)	Regular menstrual cycle (n = 116)	p-value
Unadjusted (mean ± SE)	34.3 ± 0.79	31.9 ± 0.67	0.025
Adjusted for age and relationship duration (mean ± SE)	36.1 ± 1.16	34.2 ± 1.13	0.073
Adjusted for age, relationship duration and migraine status (mean ± SE)	35.1 ± 1.18	33.4 ± 1.14	0.081

Discussion

Premenopausal women with migraine in a relationship have significantly higher jealousy scores than controls in this study. This is independent from whether they experience menstrually-related attacks and the effect disappears after menopause. Our hypothesis is that this association between migraine and increased jealousy is due to the effect of estrogen. Previous research showed estrogen levels to be higher in women with MM compared to controls during most phases of the menstrual cycle, and with only small differences between MM and non-MM patients.[7,8] As estrogen levels will be low in the postmenopausal stage of life we expected that difference in jealousy levels would diminish and indeed we did not find differences when comparing postmenopausal female migraine patients with controls supporting our hypothesis. Interestingly, we did not find a significant difference in jealously between patients with menstrually-related attacks (MM) and those without menstrually-related attacks (non-MM). We imagine that there might be one important explanation for this, namely the inaccuracy of non-diary self-reported MM or non-MM diagnosis. In a recent study, we asked 104 female migraine patients whether their attacks were associated with the menstruation and then collected prospective E-diaries. In this study, we showed women's self-reported diagnoses had a positive predictive value of 65% and negative predictive value of 50%. Sensitivity was 80% and specificity 33%.[22] Accurate MM diagnoses are difficult to obtain even when prospective diaries are collected. Previous research has shown that current ICHD-3 diagnostic criteria for MM reached maximum sensitivity only for three menstrual cycles, although specificity increased with more cycles of data collection.[23] Thus, accuracy of self-reported menstrual-related migraine diagnosis is poor in female migraine patients and we suggest to reconsider the IHCD-3 criteria for menstrual migraine where no prospective diary data is required anymore to confirm MM.

Are there alternative explanations for our findings? The effect of a disabling chronic disease on the quality of life might explain the higher jealousy response within romantic relationships in female migraine patients. The most recent Global Burden of Disease study ranked migraine as the second most disabling disease worldwide.[24] Previous studies showed that migraine patients scored lower on health-related quality of life domains than controls, such as social functioning and mental health.[25,26] Female migraine patients might have less social interaction compared to their partners, both during a migraine attack due to severe headache and disabling associated symptoms, but also outside migraine attacks due to an adjusted lifestyle trying to prevent migraine attacks. One could imagine that a disbalance in social interactions in a romantic relationship may induce jealousy towards a partner. Studying the association between other disabling chronic diseases and jealousy within romantic relationships may be of interest in this light. Although postmenopausal women with migraine are limited in social activities, their jealousy response is comparable to that of postmenopausal controls, suggesting that impaired social functioning only partially contributes to the difference in jealousy between younger migraine patients and controls. Several population-based studies have analysed the prevalence of disabling pain disorders and associated risk factors. Separated or divorced status is consistently associated with an increased risk of (chronic) pain in women.[27-29] Additionally, separation and divorce have been suggested to be a risk factor for worsening outcomes in pain disorders with persisting pain.[30] This knowledge might be helpful in understanding the potential adverse effects of migraine on the relationships of patients, such as jealousy and potentially divorce.

A recent meta-analysis on personality of migraine patients has shown higher risk for neuroticism and harm avoidance, and for low self-directedness and extraversion in migraineurs,[31] which hypothetically may be involved in more pronounced reactive and anxious jealousy scores than preventive scores for MM patients.

Women using combined oral contraceptives reported higher jealousy compared to non-using women with a regular menstrual cycle, which is congruent with previous studies.[13,20] With this, our study contributes to the existing literature by using a different study population and adjusting for relevant covariates, which limits potential confounders and increases the validity. Participants in our study were older and had a longer relationship duration compared to participants in other studies, who were students between the age of 22 and 33 years with a mean relationship duration of one year.[13,20] The higher jealousy levels in women using combined oral contraceptives might be caused by an effect of estrogen, which is suggested to influence jealous behavior.[14,15] Progesterone dose in combined

oral contraceptives is shown to be unrelated to reported jealousy, but combined oral contraceptives with higher doses of ethinyl estradiol are associated with higher jealousy compared with formulations with lower ethinyl estradiol doses.[14,15]

This study has a number of strengths. A large number of participants from the reliable LUMINA cohort were recruited. Furthermore, a validated jealousy scale was used, with a Cronbach's alpha of 0.843 indicating a very good internal consistency. However, some limitations of our study should be mentioned. Firstly, a considerable part of invited women were classified as non-responders. The non-response rate could partially be explained by women who were not eligible for participation, e.g. as they had no romantic partnership at the time of the study but refrained from informing the investigators. Secondly, as indicated the MM and non-MM diagnoses in this study were not based on diary data as this is not a requirement anymore in the ICHD-3 classification. In addition, the phase of the menstrual cycle at the time of completing the questionnaire is unknown. In a prior study, higher jealousy levels were found in the fertile phase compared to the non-fertile phase of the menstrual cycle. However, this effect became marginally significant when comparing the menstrual cycle phases in partnered women.[13] Since we included only partnered women, this is thus thought to be of less importance for our results. Additionally, since the percentage of women with a regular menstrual cycle in the MM and control group is comparable (41% vs. 42% respectively), the amount of women in the fertile and non-fertile phase is expected to be equally distributed in these groups.

Conclusions

Our study is the first to show that young migraine women are more jealous within a romantic partnership than non-migraine women. We suggest estrogen to play an important role in this relationship. Future research is needed on establishing the role of estrogen in women with migraine as this may provide important treatment options for this incapacitating disorder. We encourage physicians treating patients with migraine to pay attention to aspects of social functioning.

Abbreviations: COC: combined oral contraceptives; LUMINA: Leiden University Medical Centre MIgraine Neuro Analysis; MM: menstrual migraine; MRM: menstrually-related migraine; non-MM: non-menstrual migraine; PMM: pure menstrual migraine

Authors' contributions: DvC and GT contributed to the study design. DvC and FvW were responsible for running the study. DvC carried out the statistical analyses with help from

FvW. All authors contributed to the interpretation of the results. DvC made the figures and wrote the initial draft of the manuscript. FvW, GT and AMvdB critically revised the article, and all authors approved the final version for submission.

Ethics approval and consent to participate: The study was approved by the medical ethics committee of Leiden University Medical Center (METC number P12.201). All subjects provided written informed consent prior to the study.

Availability of data and material: Data not published within the article is available from the corresponding author on reasonable request.

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Competing interests: The authors declare that they have no competing interests deemed relevant to the manuscript.

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Online supplementary information

LUMINA Background information

Dutch migraine patients aged 18-80 years were recruited via nationwide public announcement, advertising in lay press and our research website (www.lumc.nl/hoofdpijn). They were considered eligible after a two-step inclusion process using validated questionnaires via the dedicated Leiden University MIgraine Neuro-Analysis (LUMINA) website. Additionally, patients attending our outpatient headache clinic were invited to participate by a letter. Patients were first asked to fill out a validated web-based screening questionnaire with a sensitivity of 0.93 and specificity of 0.36.[1] Patients who fulfilled the screening criteria, were sent a validated web-based extended migraine questionnaire[2], based on the International Classification of Headache Disorders criteria (previously ICHD-2, now ICHD-3 version) criteria.[3] The specificity of the second questionnaire was 0.95 and sensitivity was 0.45.[2] This questionnaire is accessible for patients via our research website and is described in English in detail by van Oosterhout et al. 2011.[2] We consider the cohort a well-defined web-based cohort. Four percent of subjects were included from our headache outpatient clinic and 87% of the participants were previously diagnosed with migraine by a physician. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, aura and headache characteristics, acute and prophylactic headache medication use, and allodynia. Participants unable to use the web-based questionnaires due to lack of the needed internet skills were allowed to fill out the questionnaires on paper.

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CHAPTER 7

General Discussion

In this thesis, clinical manifestations of sex hormonal influences in migraine are investigated by examining clinical sex differences and female-specific characteristics.

Part I: Clinical sex differences in migraine

Only little attention has been paid to sex differences in previous migraine-related research, which seems surprising given the large influence of sex on migraine prevalence. However, analysing results separately for men and women is often complicated by a lack of statistical power in individual studies due to low numbers of included men. This obstacle should be overcome since knowledge on differences in migraine characteristics and treatment response between men and women may increase understanding of underlying pathophysiological mechanisms such as the role of sex hormones and may contribute to sex-specific migraine treatment approaches. In this thesis, two studies are described on migraine-related sex differences, one on the effect of sex on the clinical response to triptans and another on sex differences in the prevalence of migraine trigger factors.

Sex differences in clinical response to triptans

Triptans are the most widely prescribed acutely acting migraine-specific treatments in both sexes. As a majority of women have been included in clinical trials evaluating the efficacy of triptans, the statistical power to study the effect of sex on triptan response has often been limited in individual studies. Chapter 2 describes a systematic review and meta-analysis investigating whether sex is an important determinant in the clinical response to triptans. In addition, sex differences in clinical response outcomes were related to sex-specific values of pharmacokinetic parameters.

Remarkably few studies presented the results of clinical trials with triptans separately for men and women. The available studies showed that women had a higher drug exposure, appearing from a higher peak drug concentration and area under the curve, which was reflected by equally good 2 hour response rates in men and women. The higher drug exposure in women was also reflected by a higher adverse event frequency after the intake of triptans than men. Despite higher drug exposure, women had higher headache recurrence rates, which was hypothesized to be due to menstrually related migraine attacks that are provoked by sex hormonal changes and tend to have a longer duration. This hypothesis was confirmed by the comparison of menstrually related migraine attacks and non-menstrually related migraine attacks based on an electronic diary (E-diary) study

presented in **chapter 5**, showing that menstrually related migraine attacks indeed had a longer duration and a higher risk of migraine recurrence within 24 and 48 hours. It can also be hypothesized that migraine attacks provoked by sex hormonal changes during perimenopause may contribute to the observed higher headache recurrence rates in women.

Physicians treating patients with migraine should be aware that dose reduction in order to reduce adverse events is undesirable, because this might further increase the risk for headache recurrence in women and might also affect initial efficacy.

Sex differences in prevalence of migraine trigger factors

The susceptibility to migraine attacks is suggested to be determined by natural fluctuations in neuronal excitability in the brain due to a complex interaction between internal threshold modulating factors and external modifiable factors. The internal threshold components are partly stable, such as genetic predisposition factors, and partly fluctuating, such as sex hormonal conditions.[1,2] External modifiable factors may trigger an attack especially when the threshold is already low, e.g. during a menstruation or after a period of sleep deprivation. **Chapter 3** presents a large cross-sectional study investigating sex differences in the prevalence of migraine trigger factors.

The top three most reported trigger factors in women were menstruation, stress, and exposure to bright light. Men reported stress, bright light, and sleep deprivation most frequently as provoking factors. Women reported more migraine trigger factors than men, even when menstruation was disregarded. It can be hypothesized that sex hormonal differences between men and women contribute to a different pattern of fluctuations in neuronal brain excitability and the internal migraine threshold, and therefore, to an increased potential of external trigger factors to provoke migraine in women. This hypothesis is supported by the finding that the total number of reported trigger factors by postmenopausal women with stabilized sex hormones was comparable to that in men.

For future studies it may be interesting to incorporate detailed information on triggers and attack occurrence as migraine patients may wrongly interpreted premonitory symptoms for triggers. As an example, migraine patients may perceive factors as bright sunlight and stress more intensely during the premonitory phase as a result of an enhanced neuronal susceptibility.[3]

The pathophysiological role of sex hormones in women with migraine

Besides obviously important peripheral neurovascular effects, estrogen and progesterone have opposite effects on neuronal excitability, with estrogen being excitatory and progesterone being inhibitory, which may have a role in modulating susceptibility to menstrual cycle-related disorders, such as menstrually related migraine and premenstrual syndrome.[4,5] Therefore, the observation that the onset of menstrually related migraine attacks is correlated with falling levels of estrogen seems counterintuitive.[1,6] Possibly, the rate of estrogen decline is implicated and estrogen withdrawal may only provoke a migraine attack after several days of high levels.[7,8] The exact underlying mechanisms remain unknown, but it is hypothesized that fluctuations in estrogen levels influence several regions of the trigeminovascular system, which is the main pathway involved in migraine.[5,9,10]

High concentrations of estrogen and progesterone receptors are located in the hypothalamus,[11] and sex hormonal fluctuations are suggested to induce an abnormal hypothalamic activation during migraine in women.[12,13] Although the pathophysiological role of the hypothalamus as generator of the trigeminal pain system is not undisputed, several hypothalamic descending projections have been shown to modulate trigeminovascular nociceptive processing.[14] In addition, imaging studies revealed that the hypothalamus is activated during the premonitory and headache phase of migraine attacks, and typical migraine premonitory symptoms such as fatigue and yawning, but also the association of attacks to circadian and menstrual cycles could be explained by involvement of the hypothalamus.[13,15-19] Fluctuations of estrogen levels also were shown to modulate calcitonin gene-related peptide (CGRP) in the trigeminovascular system.[20] CGRP is believed to play a key role in migraine pathophysiology by causing vasodilation of dural and pial vessels, mediating neurogenic inflammation, and transmission of nociceptive information from intracranial blood vessels to the central nervous system.[14,21] The periaqueductal gray is another region of the trigeminovascular system that is involved in the modulation of nociceptive responses, of which the output is enhanced by excitatory effects of estrogens that act on GABA-ergic neurons.[10,14]

Also cortical spreading depression (CSD), which is thought to be the underlying mechanism of the migraine aura is suggested to be affected by estrogen levels. High estrogen levels were shown to increase CSD susceptibility, whereas estrogen withdrawal and low estrogen levels appeared to decrease the risk for CSD.[22] This may explain why menstrually related migraine attacks are less likely to be associated with an aura as described in **chapter 5**.

The menopausal transition phase is also associated with an increased migraine prevalence, which is hypothesized to be provoked by estrogen withdrawal due to prolonged periods of amenorrhoea.[23-26] In this estrogen-deficient state, there is increased expression of neuropeptides within the infundibular nucleus of the hypothalamus, such as neurokinin B, which increases the pulsatile secretion of gonadotropin-releasing hormone (GnRH) and is involved in the susceptibility to vasomotor symptoms.[27-29] Pathophysiological involvement of neuropeptides such as neurokinin B in women with migraine during perimenopause might also be suggested because these hormones seem to be expressed in the trigeminovascular system and vasomotor symptoms have been reported to be more common in women with migraine.[23,27,30] Interestingly, targeting neurokinin B might thus be helpful in perimenopausal women with migraine, as it has also been shown to be effective in hot flushes.[31]

Part II: Clinical female-specific characteristics of migraine

The second part of this thesis focuses on the investigation of clinical female-specific characteristics of migraine. Sex hormonal changes during the luteal phase of the menstrual cycle increase the risk for menstrually related migraine attacks and also have been suggested to provoke symptoms of premenstrual syndrome.[32,33] Due to the strictly defined temporal relationships between both disorders and the menstruation, prospective diaries are needed to reliably confirm diagnoses of menstrually related migraine and premenstrual syndrome.[34,35] Moreover, there is a need for a high standard regarding the reliability of data in research and in clinical practice, which also requires daily diary registrations to reduce recall bias.[36] Therefore, a self-developed E-diary was introduced, which enabled obtaining reliable data on migraine-related outcomes, comparing migraine characteristics between menstrually related attacks and non-menstrually related attacks and determining the prevalence of premenstrual syndrome in women with migraine. Lastly, the association between romantic relationship jealousy and migraine was assessed in women since estrogen is suggested to play a major role in both conditions.

Introduction of an electronic headache diary

Most available daily E-diaries for migraine lack specificity as they fail to determine whether a reported day was fulfilling the ICHD-3 criteria for migraine and/or headache. In **chapter 4** a self-developed time-locked E-diary is described, including an automated algorithm differentiating headache and migraine days based on detailed characteristics

according to ICHD-3 criteria. The E-diary showed usefulness in diagnosing migraine when added to two previously validated headache E-questionnaires. Making diagnoses prior to a first consultation at the Headache Clinic has great relevance in a new era of emerging telemedicine. Additionally, the need for E-diaries to obtain reliable information was emphasized as patients did not reliably recall migraine-related frequency numbers, indicating that clinical decision making based on information from patients' memory is not recommended. The implementation of E-diaries in clinical headache practice could be indicative for other health care providers (e.g. GP's, general neurology practices and specialized headache clinics) that recently have been confronted with the need for telemedicine approaches and offers opportunities for research.

Differences between menstrually related and non-menstrually related attacks

Although some small and medium-sized diary-based studies suggested that menstrually related migraine attacks have a longer duration, are less responsive to acute therapy and are more likely associated with disability compared to non-menstrually related migraine attacks, the results of different studies have been inconsistent.[37-40] Therefore, in **chapter 5** the self-developed E-diary was used to perform a large prospective observational study aiming to provide conclusive results on differences in migraine characteristics between menstrually related attacks and non-menstrually related attacks. Menstrually related migraine attacks showed to have a longer duration with a higher risk of migraine recurrence compared to non-menstrually related attacks, which probably explains the observed higher recurrence rates after the use of triptans in women than in men as described in **chapter 2.** Additionally, menstrually related attacks were associated with a higher headache intensity, more pronounced photophobia and phonophobia, and decreased pain coping. The longer duration of menstrually related attacks with higher recurrence rates probably resulted in the observed increased use of triptans. Lastly, menstrually related migraine attacks were less frequently accompanied by auras, but no differences were observed on 2 hour triptan response rates, nausea, vomiting and the use of analgesics. Results of **chapter 2** showed that women have a higher triptan exposure compared to men, which is reflected by equally good 2 hour response rates in both sexes. Therefore, the similar 2 hour response rates in menstrually related and non-menstrually related attacks were in accordance with expectations.

Premenstrual syndrome and migraine

Several hypotheses have been formulated on an important role of the hypothalamic–pituitary–gonadal axis in premenstrual syndrome. It has been suggested to be triggered

by decreasing progesterone levels during the late luteal phase because progesterone regulates the expression of the GABA(A) receptor.[41] Others suggest that premenstrual symptoms are provoked by the preovulatory peak in estradiol and/or by the postovulatory increase in progesterone.[42,43] The sex hormone sensitivity hypothesis suggests that women with premenstrual syndrome have an altered sensitivity to normal sex hormonal fluctuations at the receptor level.[44-47] Growing evidence suggests that affective symptoms of premenstrual syndrome reflect suboptimal GABA(A) receptor sensitivity to fluctuating levels of the positive modulator allopregnanolone.[48] Allopregnanolone is a neuroactive metabolite of progesterone and has an inhibitory effect on neuronal excitability.[49] Reduced levels of allopregnanolone have been associated with the development of depressive disorders and menstrual cycle-related disorders.[50] However, lower allopregnanolone levels following antidepressant treatment for severe premenstrual syndrome were shown to be associated with improvement of mood and behavioural symptoms.[51] In addition, subcutaneous injections with allopregnanolone antagonists during the luteal phase have shown promising results as a potential treatment for premenstrual dysphoric disorder, which is a severe form of premenstrual syndrome.[52] Recently, attention has also been paid to the role of allopregnanolone in women with menstrually related migraine. So far, conflicting results were observed regarding differences in serum allopregnanolone concentrations between women with migraine and women without migraine.[53,54] Allopregnanolone as a potential target in premenopausal women with migraine should be explored, especially in women who are also suffering from premenstrual syndrome.

Findings of previous small diary-based studies and retrospective cross-sectional studies on the existence of a comorbidity between menstrually related migraine attacks and premenstrual syndrome have been contradictory.[55-58] The large prospective observational E-diary study from **chapter 5** was also used to determine the prevalence of premenstrual syndrome as comorbidity in women with migraine. Premenstrual syndrome prevalence in women with migraine appeared to be comparable to the prevalence in the general population. Fulfilling criteria of menstrually related migraine did not affect premenstrual syndrome prevalence, which suggests that the provoking factor of sex hormonal changes during the luteal phase of the menstrual cycle is different in both disorders. Research on premenstrual syndrome in women with migraine is complicated by corresponding symptomatology of premenstrual syndrome, the premonitory phase of migraine attacks and symptoms of depression, which is strongly associated with migraine.

Jealousy in women with migraine

Estrogen plays a role in the susceptibility to migraine attacks and it has been suggested to affect jealousy in romantic relationships in women. In the fertile phase, when estrogen levels are high, women tend to report higher jealousy levels compared to other times of the menstrual cycle.[59] Furthermore, jealousy seems to be affected by the use of combined oral contraceptives. Especially using formulations with higher doses of ethinyl estradiol are associated with significantly higher jealousy scores.[60] Therefore, it could be hypothesized that women with migraine may be more jealous than women without migraine. In **chapter 6**, the association between romantic relationship jealousy and migraine is evaluated based on a validated jealousy questionnaire in premenopausal and postmenopausal women who were in a heterosexual or homosexual relationship. Premenopausal women with migraine showed to be more jealous in a romantic relationship compared to controls. This seemed independent from whether they experienced menstrually related attacks, although it should be noted that menstrually related migraine was not assessed with an E-diary. The difference in jealousy levels disappeared after menopause, which was hypothesized to be due to low and stabilized estrogen levels. However, another explanation may be that postmenopausal women have more long-lasting romantic relationships than younger migraine women who might be at the start of their relationships and still have to build trust in their partners.

Conclusions

Female-specific sex hormonal conditions are suggested to contribute to a lower internal migraine threshold, increasing the risk for menstrually related migraine attacks and potentiating the provoking effect of external trigger factors. Daily E-diary registrations are needed to correctly define menstrually related migraine attacks and to reliably determine migraine-related frequencies. Based on E-diary data, menstrually related migraine attacks were shown to have a longer duration with a higher risk of migraine recurrence, increased headache intensity, and decreased pain coping compared to non-menstrually related attacks. While women more often experienced adverse events after the intake of triptans than men due to a higher drug exposure, an increased intake was seen during menstrually related attacks compared to non-menstrually related attacks. The long attack duration of menstrually related migraine attacks with a high risk of recurrence may be the explanation for higher migraine recurrence rates after the use of triptans in women compared to men.

Future perspectives

The long duration of menstrually related migraine attacks with high risk of recurrence and reduced pain coping abilities emphasize the need to improve the understanding of the provoking role of sex hormones in women with migraine. The change in estrogen levels prior to the menstruation, possibly the rate of decrease in estrogen, is implicated in an increased susceptibility to migraine attacks,[8] but the exact provoking effect of sex hormonal changes remains unknown since the association with the occurrence of migraine attacks has often been undefined. A large case-control study is needed, not only examining absolute sex hormone levels during several time points of the luteal phase, but also ratios of sex hormones and the rate and amplitude of changes in sex hormone levels. Levels of metabolites of estrogen and progesterone, such as allopregnanolone and pregnenolone (sulfate), should also be investigated during the same time points to explore its potential role in women with migraine. Furthermore, CGRP measurements should not me omitted, because of its important role in the pathophysiology of migraine and results of previous studies have suggested that levels might be affected by sex hormones.[61-63] Apart from the above-mentioned hormone measurements, which all focus on sex aspects, also measurements of gender are of importance, since gender-related factors may influence the way symptoms are reported by patients. Such measurements should be accompanied by daily E-diary registrations in order to provide insight in the temporal relationship between specific sex hormonal findings and the occurrence of menstrually related migraine attacks. A similar case-control study with perimenopausal women could contribute to an increased understanding of the role of changing sex hormonal conditions in women with migraine during menopausal transition. In this group, it would be interesting to obtain information on the presence of climacteric symptoms and to add neurokinin B measurements, because of its involvement in the pathophysiology of vasomotor symptoms, and potentially, in migraine during perimenopause. Ultimately, all this knowledge will contribute to the development of an urgently needed female-specific prophylactic treatment intervening with sex hormones. To begin with, the potential efficacy of existing hormonal treatments, such as combined oral contraceptives, in the prevention of migraine attacks should be clarified.

Female migraine patients appeared to be poor at indicating whether the menstruation is a consistent trigger for their migraine attacks,[35] which suggests that confirmation of a close temporal relationship between other suspected trigger factors and the onset of migraine attacks based on E-diary registrations will improve the accuracy of trigger-related research.

Additionally, it would be interesting to investigate the triggering effect of perceived trigger factors throughout the menstrual cycle in order to test the hypothesis that sex hormonal fluctuations related to the menstruation and ovulation contribute to a lower internal migraine threshold, increasing the potential of external trigger factors to provoke migraine in women.

Trigger-related research is complicated by overlap of trigger factors and premonitory symptoms as some putative trigger factors might in fact be part of the premonitory symptom phase reflecting an already started attack. Symptomatology of premenstrual syndrome and the premonitory phase also partly correspond, which further complicates research on these topics. Large scale collection of daily E-diary data on the exposure to trigger factors and the experience of symptoms belonging to the premonitory phase and/or premenstrual syndrome offers possibilities for artificial intelligence approaches to determine their contribution in the prediction of an upcoming migraine attack. An algorithm may detect a pattern of features that specifically occur prior to the headache phase of menstrually related migraine attacks. However, the interpretation of obtained results and defining its implications will probably remain challenging.

Understandably, a majority of women is included in clinical trials on the efficacy and tolerability of acute and preventive migraine treatments. However, migraine researchers should be encouraged to analyze and present data by sex, because that will eventually enable researchers to perform meta-analyses investigating whether sex is an important determinant in the clinical response to these treatments.

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CHAPTER 8

Summary

Nederlandse Samenvatting

Summary

This thesis explores clinical manifestations of sex hormonal influences in migraine with the ultimate goal to increase the understanding of the role of sex hormones in women and to contribute to the effectuation of sex-specific migraine treatment approaches. The research is divided in two parts. **Part I** describes studies examining clinical sex differences in migraine, and **Part II** describes studies focussing on clinical female-specific characteristics of migraine.

Part I starts with a description of a systematic review and meta-analysis in **chapter 2**, investigating sex differences in the efficacy of triptans. Remarkably, few authors presented their results of clinical trials with triptans separately for men and women. Based on the available data, a higher adverse event frequency after the intake of triptans was observed in females compared to males, which may be due to a combination of a higher drug exposure and a larger tendency to report adverse drug reactions. Despite higher drug exposure, women more often experienced headache recurrence after an initially adequate triptan response, which is probably due to the occurrence of menstrually related migraine attacks that generally have a longer duration. Physicians are advised not to apply a dose reduction in order to reduce adverse events in women, because this might further increase the risk for headache recurrence and may also affect initial efficacy.

Chapter 3 describes a large cross-sectional study investigating sex differences in the prevalence of migraine trigger factors. The top three most reported trigger factors in women were menstruation, stress, and exposure to bright light. Men reported stress, bright light, and sleep deprivation most frequently as provoking factors. Furthermore, women reported more migraine trigger factors than men, also after disregarding menstruation. It is suggested that female-specific sex hormonal fluctuations contribute to a lower internal migraine threshold, and therefore, to an increased potential of external trigger factors to provoke migraine attacks in women.

Part II starts with an introduction of a self-developed electronic diary (E-diary) in **chapter 4**, including an automated algorithm differentiating headache and migraine days based on detailed characteristics according to ICHD-3 criteria. The E-diary showed usefulness in diagnosing migraine prior to a first consultation at the Headache Clinic when added to two previously validated headache E-questionnaires. In addition, the need for E-diaries

to obtain reliable information is emphasized as patients did not reliably recall monthly migraine-related frequency numbers.

Chapter 5 describes a large prospective observational E-diary study, investigating differences in migraine characteristics between menstrually related attacks and non-menstrually related attacks. In addition, the prevalence of premenstrual syndrome as comorbidity in women with migraine is determined. Menstrually related migraine attacks showed to have an increased headache intensity and a longer duration with a higher risk for headache recurrence compared to non-menstrually related attacks, which probably explains the increased use of triptans during menstrually related attacks. Menstrually related attacks were less frequently associated with auras, but no differences were observed on 2 hour triptan response rates, nausea, vomiting and the use of analgesics. The prevalence of premenstrual syndrome in women with migraine was comparable to the prevalence in the general population. Fulfilling criteria of menstrually related migraine did not affect premenstrual syndrome prevalence, which suggests that the provoking factor of sex hormonal changes during the luteal phase of the menstrual cycle is different in both disorders.

Estrogen plays a role in the susceptibility to migraine attacks and it has been suggested to affect jealousy in romantic relationships in women. In Chapter 6 a case-control study is presented, comparing jealousy levels within romantic relationships between women with migraine and controls. Premenopausal women with migraine showed to be more jealous compared to controls, which was independent from whether they experienced menstrually related attacks. The difference in jealousy levels disappeared after menopause, possibly due to low and stabilized estrogen levels. It is suggested that estrogen plays an important role in the relationship between migraine and jealousy, which stresses the need to elucidate the exact role of estrogen in women with migraine.

Finally, chapter 7 provides a general discussion and suggests possibilities for future research.

Nederlandse Samenvatting

In dit proefschrift worden de klinische uitingen van de invloed van geslachtshormonen in migraine onderzocht, met als uiteindelijk doel de kennis over de rol van geslachtshormonen bij vrouwen te vergroten en bij te dragen aan het realiseren van sekse-specifieke behandelstrategieën. Het onderzoek is opgesplitst in twee delen. **Deel I** beschrijft studies waarin klinische sekse verschillen in migraine worden onderzocht, en **deel II** beschrijft studies over klinische vrouwspecifieke kenmerken van migraine.

Deel I begint met een beschrijving van een systematische review en meta-analyse in **hoofdstuk 2,** waarbij is gekeken naar sekse verschillen in de effectiviteit van triptanen. Opmerkelijk weinig auteurs hebben de resultaten van klinische onderzoeken met triptanen gescheiden voor mannen vrouwen gepresenteerd. Op basis van de beschikbare gegevens werd geconcludeerd dat vrouwen vaker bijwerkingen ervaren na de inname van triptanen dan mannen, wat mogelijk komt door een combinatie van een grotere blootstelling aan het geneesmiddel en een grotere neiging om bijwerkingen te rapporteren. Ondanks de grotere blootstelling kwam de hoofdpijn bij vrouwen vaker terug nadat een triptan tijdelijk goed effect had, wat waarschijnlijk komt door het optreden van menstruatie-gerelateerde migraine aanvallen die over het algemeen langer duren. Dokters worden geadviseerd niet de dosis te verlagen om bijwerkingen bij vrouwen te verminderen, omdat dit het risico op terugkeer van hoofdpijn verder kan verhogen en mogelijk ook de initiële effectiviteit kan beïnvloeden.

Hoofdstuk 3 beschrijft een groot cross-sectioneel onderzoek naar sekse verschillen in de prevalentie van migraine triggerfactoren. De drie meest gerapporteerde triggerfactoren bij vrouwen waren de menstruatie, stress en blootstelling aan fel licht. Mannen rapporteerden stress, fel licht en slaapgebrek als meest voorkomende uitlokkende factoren. Verder rapporteerden vrouwen meer migraine triggerfactoren dan mannen, ook wanneer de menstruatie buiten beschouwing gelaten werd. Er wordt gesuggereerd dat vrouwspecifieke schommelingen in geslachtshormonen bijdragen aan een lagere interne migraine drempel, waardoor externe triggerfactoren makkelijker een migraine aanval kunnen uitlokken bij vrouwen.

Deel II begint met een introductie van een zelfontwikkeld elektronisch dagboek (E-dagboek) in **hoofdstuk 4**, dat met een geautomatiseerd algoritme onderscheid maakt tussen hoofdpijn- en migrainedagen op basis van gedetailleerde kenmerken volgens de ICHD-3 criteria. Het E-dagboek bleek bruikbaar te zijn voor het stellen van een migraine diagnose

voorafgaand aan een eerste consult op de Hoofdpijnpolikliniek wanneer het samen met twee eerder gevalideerde hoofdpijn E-vragenlijsten wordt toegepast. Bovendien wordt benadrukt dat het gebruik van E-dagboeken noodzakelijk is om betrouwbare informatie te verkrijgen, omdat patiënten zich maandelijkse migraine gerelateerde aantallen niet goed konden herinneren.

Hoofdstuk 5 beschrijft een grote prospectieve observationele E-dagboekstudie waarin de verschillen in klinische migraine kenmerken tussen menstruatie-gerelateerde aanvallen en niet-menstruatie-gerelateerde aanvallen worden onderzocht. Daarnaast werd de prevalentie van het premenstrueel syndroom als comorbiditeit bij vrouwen met migraine bepaald. Menstruatie-gerelateerde aanvallen hadden een hogere hoofdpijnintensiteit en een langere duur met een hogere kans op terugkeer van hoofdpijn dan niet-menstruatie-gerelateerde aanvallen, wat waarschijnlijk het hogere gebruik van triptanen tijdens de menstruatie-gerelateerde aanvallen verklaart. Menstruatie-gerelateerde migraine aanvallen gingen minder vaak gepaard met aura's, maar er werden geen verschillen gevonden in de effectiviteit van triptanen na 2 uur, misselijkheid, braken en het gebruik van analgetica. De prevalentie van premenstrueel syndroom in vrouwen met migraine was vergelijkbaar met de prevalentie in de algemene bevolking. Het voldoen aan de criteria van menstruatie-gerelateerde migraine had geen effect op de premenstrueel syndroom prevalentie, wat suggereert dat de uitlokkende factor van de veranderingen in geslachtshormoonlevels tijdens de luteale fase van de menstruatiecyclus bij beide aandoeningen verschillend is.

Oestrogeen speelt een rol in de gevoeligheid voor migraine aanvallen en het lijkt bij vrouwen ook invloed te hebben op de mate van jaloezie in een romantische relatie. In **hoofdstuk 6** wordt een case-control onderzoek gepresenteerd waarin de mate van jaloezie in een romantische relatie wordt vergeleken tussen vrouwen met migraine en vrouwen zonder migraine. Premenopauzale vrouwen met migraine bleken jaloerser te zijn dan vrouwen zonder migraine, wat onafhankelijk was van het optreden van menstruatie-gerelateerde migraine aanvallen. Het verschil in de mate van jaloezie verdween na de menopauze, mogelijk door lage en gestabiliseerde oestrogeenlevels. Er wordt gesuggereerd dat oestrogeen een belangrijke rol speelt in de relatie tussen migraine en jaloezie, wat benadrukt dat de exacte rol van oestrogeen in vrouwen met migraine opgehelderd moet worden.

Ten slotte wordt in **hoofdstuk 7** een algemene discussie gepresenteerd en worden mogelijkheden voor toekomstig onderzoek voorgesteld.

APPENDICES

List of Publications

PhD Portfolio

Curriculum Vitae

Dankwoord

List of Publications

I.E. Verhagen, D.S. van Casteren, S. de Vries Lentsch, G.M. Terwindt. Effect of lockdown during COVID-19 on migraine: a cohort study. *Cephalalgia 2021;* [Epub ahead of print].

D.S. van Casteren, T. Kurth, A.H.J. Danser, G.M. Terwindt, A. MaassenVanDenBrink. Sex differences in response to triptans: a systematic review and meta-analysis. *Neurology* 2021;96:162-170

D.S. van Casteren, I.E. Verhagen, G.L.J. Onderwater, A. MaassenVanDenBrink, G.M. Terwindt. Sex differences in prevalence of migraine trigger factors: a cross-sectional study. *Cephalalgia* 2020; [Epub ahead of print].

K.M. Linstra, K. Ibrahimi, D.S. van Casteren, M.J.H. Wermer, G.M. Terwindt, Antoinette MaassenVanDenBrink. Pain perception in women with menstrually-related migraine. *Cephalalgia* 2020; [Epub ahead of print].

D.S. van Casteren, A. MaassenVanDenBrink, G.M. Terwindt. Migraine and other headache disorders in pregnancy. In: Steegers EAP, Cipolla MJ, Miller EC (Eds). *Neurology and Pregnancy: Neuro-Obstetric Disorders*, Volume 172. San Diego: Elsevier BV, 2020:187-199.

D.S. van Casteren, F.A.C. van Willigenburg, A. MaassenVanDenBrink, G.M. Terwindt. Jealousy in women with migraine: a cross-sectional case-control study. *The Journal of Headache and Pain* 2020;21:51-58.

D.S. van Casteren, E.G.M. Couturier, A. MaassenVanDenBrink. Sex- and gender-specific aspects of migraine treatment. In: MaassenVanDenBrink A and MacGregor EA (Eds). *Gender & Migraine.* Springer Nature; 2019:31-43.

PhD Portfolio

PhD student	Daphne S. van Casteren
Department	Internal Medicine
	Division of Vascular Medicine and Pharmacology
Promotors	Prof. dr. A.H.J. Danser and Prof. dr. G.M. Terwindt
Copromotor	Dr. A. Maassen van den Brink

General academic and research skills	Year	5.2 ECTS
Introductory Meeting for PhD Candidates, LUMC, Leiden	2016	0.2
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	2016	1.0
Statistics and Journal clubs, department of Neurology, LUMC, Leiden	2016-2020	2.5
Basic Methods and Reasoning in Biostatistics, LUMC, Leiden	2017	1.5

In-depth courses		7.7 ECTS
Systematic reviews and meta-analysis, EpidM VUmc, Amsterdam	2017	1.2
Hoofdpijn IN-zicht, LUMC, Leiden	2017	0.3
iHead Meeting, The International Headache Society, London	2016	1.0
Regression Analysis, LUMC, Leiden	2019	1.5
Repeated Measurements, LUMC, Leiden	2019	1.5
iHead Meeting, The International Headache Society, Dublin	2019	1.0
Using R for Data Analysis, LUMC, Leiden	2019	1.2

Presentations		4.0 ECTS
Gender en Gezondheid, WOMEN Inc congress, Amersfoort *The Migraine-WHAT! Study - Women, Hormones, Attacks and Treatment* (Poster presentation)	2017	0.4
12th European Headache Federation Congress, Florence, Italy *Gender differences in clinical and pharmacological response to triptans* (Poster presentation)	2018	0.4
Science Days, Internal Medicine, Sint-Michielsgestel *Gender differences in clinical and pharmacological response to triptans* (Poster presentation)	2019	0.4
Iedere patiënt is anders, WOMEN Inc congress, Amsterdam *Gender differences in response to triptans* (Oral presentation)	2019	0.5
13th European Headache Federation Congress, Athens, Greece *Differences in sex hormone levels between female migraine patients and healthy controls* (Poster presentation)	2019	0.4
Hoofdpijn patiëntendag, LUMC, Leiden *The use of electronic headache diaries at the outpatient clinic* (Oral presentation)	2019	0.7
Gender Summit, Amsterdam *Self-reported prevalence of migraine trigger factors and patients willingness to participate in future trigger research* (Poster presentation)	2019	0.4

19th Congress of the International Headache Society, Dublin, Ireland *Gender differences in clinical and pharmacological response to triptans* (Poster presentation)	2019	0.4
Science Days Internal Medicine, Sint-Michielsgestel *Differences in sex hormone levels between female migraine patients and healthy controls* (Poster presentation)	2020	0.4

International conferences		3.0 ECT
12th European Headache Federation Congress, Florence, Italy	2018	1.0
13th European Headache Federation Congress, Athens, Greece	2019	1.0
19th Congress of the International Headache Society, Dublin, Ireland	2019	1.0

Seminars and workshops		3.5 ECTS
Wetenschappelijke jaarvergaderingen van de Nederlandse Hoofdpijn Vereniging (NHV)	2016-2019	1.0
Gender en Gezondheid, WOMEN Inc congress, Amersfoort	2017	0.3
Science Days Neurology, LUMC, Leiden	2017-2019	1.0
Sex, Drugs and Science congress, NVG&G, Rotterdam	2018	0.3
Iedere patiënt is anders, WOMEN Inc congress, Amsterdam	2019	0.3
Gender Summit, Amsterdam	2019	0.6

Teaching activities		9.0 ECTS
Minor Translational Neuroscience, LUMC, Leiden Practical teaching course - How to interview a headache patient	2017-2019	1.5
Scientific internship of bachelor medical students	2018-2019	4.0
Bachelor Medicine - Hersenen en Aansturing, LUMC, Leiden Interactive teaching courses	2019-2020	3.5

Curriculum Vitae

Daphne van Casteren was born on December 23, 1988 in Heemstede, the Netherlands. After finishing secondary school (Atheneum College Hageveld, Heemstede) in 2007, she moved to Amsterdam and started studying Biomedical Sciences at the University of Amsterdam. She passed her propaedeutic year. In 2008, she started to study Medicine at the University of Amsterdam. During medical school she completed elective internships at the Department of Paediatric Neurology of the Academic Medical Center in Amsterdam and at the Department of Neurology at Spaarne Gasthuis in Haarlem. After obtaining the degree of medical doctor in 2015 she worked as a resident (ANIOS) at the Department of Neurology at Tergooi ziekenhuis in Blaricum. From 2016 to 2020 she worked as a PhD candidate at the Department of Internal Medicine of the Erasmus Medical Center in Rotterdam and the Department of Neurology of the Leiden University Medical Center in Leiden under the supervision of Prof. dr. G.M. Terwindt, Prof. dr. A.H.J. Danser, and Dr. A. Maassen van den Brink. The results of this work are described in this thesis. From January 2021 she is working as a resident (ANIOS) at the Department of Neurology of the Leiden University Medical Center.

Dankwoord

Mijn proefschrift is klaar, wat een bijzonder moment! Dit had ik nooit alleen kunnen bereiken. Daarom wil ik om te beginnen graag mijn promotoren prof. dr. Gisela Terwindt en prof. dr. Jan Danser en mijn co-promotor dr. Antoinette Maassen van den Brink bedanken. Gisela, bedankt dat je me een rol hebt gegeven in de onderzoeksgroep waarin ik op m'n plek was, dank voor je aanstekelijke enthousiasme voor sekseverschillen in het migraineonderzoek, voor het vertrouwen in mij waardoor ik erg zelfstandig kon werken en voor je kritische blik op mijn manuscripten. Dit stimuleerde mij om het beste uit mezelf te halen. Jan, bedankt dat ik ondanks mijn beperkte aanwezigheid in het Erasmus MC werd betrokken bij de onderzoeksgroep, voor de uitnodigingen voor de wetenschapsdagen, gezellige etentjes en weekendjes weg, voor je vragen tijdens de werkbesprekingen waardoor ik werd gemotiveerd om de relevantie en betekenis van de gevonden resultaten beter toe te lichten. Antoinette, bedankt voor je prettige begeleiding die gekenmerkt wordt door je toegankelijkheid en het geven van zowel kritische als positieve feedback. Dank voor het inbrengen van een flinke dosis humor tijdens onze overlegmomenten. Met bewondering kijk ik naar je vermogen om in oplossingen te denken.

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