The Journal of Headache and Pain

CONSENSUS ARTICLE

Open Access

Sex-specific management of migraine a systematic review and consensus statement from the European Headache Federation (EHF)

Simone Braca[1†], Francesco Casillo[2†], Stefanie Moreira[3†], Esme Ekizoglu[4], Marte-Helene Bjork[5,6,7], Anna K. Szewczyk[8], Annelies Van Dycke[9], Derya Uluduz[10], Gianluca Coppola[2], Christina Deligianni[11,12], Christian Lampl[13], Erling Tronvik[7,14], Faisal Mohammad Amin[15], Jan Versijpt[16,17], Kristina Ryliškienė[18], Margarita Sanchez del Rio[19], Phil R. Holland[20], Gisela Terwindt[21], Uwe Reuter[22], Antoinette MaassenVanDenBrink[23] and Raquel Gil-Gouveia[24,25*]

Abstract

Background Migraine burden is over twice as high among females than males. Although sex differences are recognized in migraine, robust sex-specific guidance for management remains limited.

Objective To systematically review and synthesize current evidence on sex-related clinical differences in migraine, including treatment outcomes and reproductive management, and to provide evidence-based or expert consensus recommendations where high-quality data are lacking.

Methods A systematic literature review using the PICO framework addressed 24 sex-specific questions across three domains: (1) biological sex differences across the lifespan, (2) sex-specific variations in treatment outcomes, and (3) fertility and reproduction-related management. To address anticipated evidence gaps, a structured Delphi consensus process complemented the review. The protocol was registered in PROSPERO (CRD420251058438).

Results Thirty-seven studies informed 10 evidence summaries. Acute and preventive anti-CGRP therapies seem to show similar efficacy between sexes. For menstrual-related migraine attacks (MM), triptans and lasmiditan are effective, with frovatriptan being recommended for short-term prevention; long-term prevention include topiramate and anti-CGRP mAbs. In pregnancy triptans, greater occipital nerve (GON) blocks, and onabotulinumtoxinA are safe, with GON blocks showing potential efficacy. During breastfeeding, triptans appear to be safe. Anti-CGRP mAbs are equally effective in pre and postmenopausal women. Expert consensus emphasizes the influence of hormonal transitions on migraine expression across sexes and supports the use of acetaminophen, antiemetics, magnesium, NSAIDs, steroids, beta-blockers, amitriptyline, and calcium channel blockers as generally safe in WOCBP and during

[†]Simone Braca, Francesco Casillo and Stefanie Moreira contributed equally to this work.

*Correspondence:
Raquel Gil-Gouveia
rgilgouveia@gmail.com

Full list of author information is available at the end of the article

pregnancy, although some agents have trimester-specific limitations. Efficacy was noted for acetaminophen, sumatriptan, antiemetics, magnesium, propranolol, amitriptyline, and onabotulinumtoxinA. During breastfeeding, acetaminophen, NSAIDs, domperidone, prochlorperazine, magnesium, caffeine, beta-blockers, tricyclics, onabotulinumtoxinA, and GON blocks were considered safe.

Conclusions Evidence is limited, but sex (likely mediated by sex hormones) influence the clinical course of migraine, and likely treatment response. Limitations include absence of sex-specific analyses in older trials, underrepresentation of men, and scarce reproductive safety data. Integrating sex-based analyses and broadening trial inclusion and more reproductive safety evidence are essential for personalized, equitable migraine care.

Introduction

Migraine is one of the most prevalent and disabling neurological conditions globally and the most recent data from the 2023 Global Burden of Disease study shows a widening gender gap in headache-attributed health loss, with females experiencing a greater overall burden than males (2.1:1 vs. 1.6:1 in GBD 2021) [1]. The complex nature of migraine including wide phenotypic variability and polygenic inheritance has increasingly challenged the traditional one-size-fits-all approach to management and treatment. As the understanding of migraine pathophysiology increases, it is becoming evident that a personalized medicine framework is crucial to improve outcomes and reduce the burden of this disease [2].

Personalized medicine aims to tailor healthcare based on individual genetic, biological, and phenotypic characteristics. In the context of migraine, this approach is particularly pertinent as it is a disorder with different sex prevalences and in which phenotypic expression seems to be modulated by sex hormones [3]. Nevertheless, a substantial sex-related knowledge gap exists, despite the well-known differences in headache prevalence, symptoms, triggers, and management issues, between males and females. These disparities demonstrate the urgency of integrating sex (and gender) dimensions into both clinical practice and research to ensure equitable care [4].

Migraine exhibits sexual dimorphism, characterized by distinct molecular pathways and the differential regulation of neuropeptides and ion channels within the trigeminovascular system [5]. In animal models, the expression of receptor component RAMP1 of calcitonin gene-related peptide (CGRP), key mediator of migraine attacks, is markedly higher in female than in male trigeminal ganglia [6]. The trigeminovascular system is dynamically modulated by ovarian hormones, as RAMP1 expression peaks during proestrus (high-estrogen phase) and is subject to epigenetic regulation via DNA methylation [7]. Additionally, prolactin and transient receptor potential melastatin 3 (TRPM3) channels act as female-specific sensitizing factors; TRPM3-mediated firing is more prominent in female meninges, and these channels are normally inhibited by estrogen and progesterone, suggesting that hormonal withdrawal during menses disinhibits this pathway and facilitates migraine attacks [8]. Clinical studies have demonstrated that the trigeminovascular response to stimulation of Transient Receptor Potential Vanilloid 1 (TRPV1) channels differs throughout the menstrual cycle [9]. In contrast, a male-specific mechanism seems to involve orexin B and its receptor OX2R, which are more abundantly expressed in male TG and drive neuronal sensitization exclusively in males, potentially through a CGRP-independent pathway [10].

Furthermore, migraine with aura appears to be differentially influenced by sex hormones compared to migraine without aura. Increased estradiol levels during pregnancy and breastfeeding are hypothesized to enhance susceptibility to Cortical Spreading Depression (CSD), thereby triggering or worsening aura attacks [11–14]. In CACNA1A knock-in migraine mouse models, female mice show greater CSD susceptibility than males. This difference is abolished by ovariectomy and partially restored by 17β-estradiol treatment, with similar findings reported in other rodent studies [15, 16].

Additionally, CGRP-induced vasodilation of human arteries appears less potent in young women than in men, possibly due to receptor desensitization resulting from higher endogenous CGRP exposure. In contrast, TRPM3-mediated vasodilation is enhanced in females, likely reflecting higher NMDA receptor expression [17, 18].

How these sex and hormone-related biological disparities influence treatment outcomes remains unclear. Evidence regarding therapies such as CGRP-targeted monoclonal antibodies (mAbs), gepants (CGRP receptor antagonists), and triptans (serotonin 5-HT1B/1D receptor agonists) is mixed, with reported sex differences in efficacy, recurrence, and adverse events [19, 20]. Gender-affirming hormone therapy may affect migraine progression in transgender and gender non-conforming individuals, while its impact on treatment outcomes is largely unknown [21–28].

Understanding and addressing sex-specific factors may enhance our ability to customize therapies. However, the current evidence base remains limited and fragmented. To address this gap, we conducted a systematic review to synthesize existing data on sex and gender-specific approaches to migraine management and treatment. Acknowledging the anticipated scarcity of high-level

evidence, we planned to complement this analysis with expert consensus opinions, to guide clinical practice yet also to delineate priority areas requiring further research and encourage the systematic inclusion of sex-based analyses in future migraine research.

Methods

Study design and objective

A systematic literature review was conducted to investigate sex-specific differences in migraine. The review was structured according to the PICO (Population, Intervention, Comparison, Outcome) framework to define focused research questions and guide data extraction and synthesis. This strategy was designed to support the development of specific and clinically relevant evidence-based recommendations.

Given the anticipated limited availability of high-quality evidence in certain domains, a Delphi consensus panel approach was subsequently employed. The Delphi methodology was selected for its robustness in synthesizing expert opinion and promoting convergence using a structured and iterative process, enabling the formulation of expert-based recommendations in areas where evidence-based conclusions are not feasible.

The objective was to systematically and qualitatively analyze and synthesize evidence on biological sex differences in migraine in terms of clinical expression, treatment outcomes, and fertility/reproduction-specific management issues, ultimately producing clinical practice guidelines and contributing to standardized care. The protocol was developed collaboratively by the author group and has been registered in the PROSPERO database (registration number: CRD420251058438).

Working group panel composition

The European Headache Federation (EHF) board nominated a multidisciplinary working group panel. Each senior panel member collaborated with two junior headache experts from different geographic regions to enhance diversity in perspectives and ensure robust literature analysis. The panel was divided into three subgroups, each assigned PICO questions aligned with their primary areas of expertise.

Literature search strategy

Research questions were formulated using the PICO model to address specific aspects of sex-specific migraine management. During the initial meeting, the working group proposed a series of PICO-formatted research questions. These questions were refined through collective discussion and organized by consensus. A total of 24 PICO questions were developed, organized into three thematic areas: (Part I) biological sex differences in clinical expression and comorbidities, (Part II) sex differences in treatment outcomes, and (Part III) fertility and reproduction-specific management issues. The full list of PICOs is detailed in Table 1. Comprehensive searches were conducted in PubMed and Embase databases, with additional manual searches of reference lists from relevant reviews and guidelines. For Part III, safety databases and studies on migraine medications used for non-migraine indications were also included as relevant sources of data. Search terms were derived from each PICO question, combining MeSH (Medical Subject Headings) terms and free-text keywords with Boolean operators (AND, OR). Full search strings for each PICO are provided in Supplementary Material. Searches included studies published up to May 2025, ensuring inclusion of the most recent evidence.

Study selection

Three independent reviewers per PICO questioned screen titles and abstracts using the Rayyan software [29]. Eligible studies included randomized clinical trials and observational studies conducted in pediatric and adult populations. Studies were excluded if they met any of the following criteria: Population not aligned with the PICO question (e.g., non-migraine populations); Intervention not relevant to the PICO question (e.g., non-hormonal treatments for a hormonal-related PICO); No comparison between populations of interest (e.g., female vs. male or transgender female vs. male); Outcomes not relevant to the PICO question (e.g., non-migraine-related outcomes). Additionally, animal studies, case series, case reports, review articles and conference abstracts did not fit criteria for inclusion. Reasons for exclusion were documented in Rayyan to ensure transparency and reproducibility. Subsequently, eligible studies underwent full-text review by three independent reviewers to confirm inclusion based on PICO criteria. Discrepancies were resolved through consensus. For PICO questions with existing systematic reviews or meta-analyses, the "last RCT" method was applied: the most recent randomized controlled trial (RCT) from the meta-analysis was evaluated, supplemented by additional studies published after the meta-analysis cutoff date.

When individual studies that contributed to a retrieved meta-analysis also reported outcome data beyond the scope of the pooled analysis (e.g., low birthweight, uterine atony, postpartum haemorrhage, or neurodevelopmental outcomes not included in the meta-analytic estimates for PICO 20), these studies were retained in the evidence tables to provide a more comprehensive evidence summary. This approach was necessary given the scarcity and heterogeneity of reproductive safety data and to avoid the loss of clinically relevant information that would not otherwise be captured by the meta-analytic estimates alone.

Table 1 Full list of PICOs

Subgroup	PICO	Question
Part I	1	In children and adolescents with migraine, how does entering puberty influence the clinical expression of migraine in females compared to males?
Part I	2	In individuals of reproductive age with migraine, does being in the reproductive period lead to different clinical expressions of migraine in females compared to males?
Part I	3	In individuals with migraine reaching the end of the reproductive phase, how does this transition affect clinical migraine expression in females compared to males?
Part I	4	In people with migraine, how do hormonal treatments influence migraine expression in females compared to males?
Part I	5	In people with migraine, does the risk of migraine-related complications differ in females compared to males?
Part I	6	In people with migraine, how does the risk of developing chronic migraine, medication overuse and/or medication overuse headache compare between individuals of female and male sex?
Part II	7	In children and adolescents with migraine, how does puberty affect the effectiveness of acute migraine treatments in females compared to males?
Part II	8	In children and adolescents with migraine, how does puberty influence the effectiveness of preventive treatments in females compared to males?
Part II	9	Among individuals with migraine, how does long-term transgender hormonal therapy affect the effectiveness of acute migraine treatments in females compared to transgender males?
Part II	10	Among individuals with migraine, how does long-term transgender hormonal therapy influence the effectiveness of preventive migraine treatments in females compared to transgender males?
Part II	11	In adults with migraine, does the effectiveness of acute attack treatment differ between females and males?
Part II	12	In adults with migraine, does the effectiveness of preventive treatment differ between females and males?
Part II	13	In transgender individuals with migraine who are receiving long-term hormonal therapy, is there a difference in the safety of migraine treatments between transgender males and transgender females?
Part II	14	In elderly with migraine, does the effectiveness of acute attack treatment differ between females and males?
Part II	15	In elderly with migraine, does the effectiveness of preventive treatments differ between females and males?
Part III	16	In individuals with menstrual-related migraine, which treatments are effective for managing acute migraine attacks?
Part III	17	In individuals with menstrual-related migraine, which short-term treatments are effective for preventing migraine attacks?
Part III	18	In individuals with menstrual-related migraine, which prophylactic treatments are effective at preventing migraine attacks?
Part III	19	In women of childbearing potential with migraine, which treatments are safe for managing migraine?
Part III	20	In pregnant women with migraine, which treatments are safe for managing migraine?
Part III	21	In breastfeeding women with migraine, which treatments are safe for managing migraine?
Part III	22	In pregnant women with migraine, which treatments are effective for managing acute migraine attacks?
Part III	23	In pregnant women with migraine, which treatments are effective for preventing migraine attacks?
Part III	24	In post-menopausal women with migraine, which treatments are effective for managing migraine?

For PICO questions without systematic reviews, all eligible primary studies were evaluated. The sequential review steps, including the PRISMA flow diagram, are illustrated in Fig. 1.

Data extraction

Data were extracted using a standardized template, capturing study design, population characteristics, interventions, comparators, outcomes (e.g., pain freedom, migraine frequency, adverse events), and risk of bias. Extracted data were cross-checked by a second reviewer.

Data analysis

All eligible study outcome data were tabulated. A descriptive analysis was provided, summarizing study designs, populations, interventions/exposures, comparators and outcomes with counts, percentages, means ± SD or medians (IQR) as appropriate. When suitable, a meta-analytic approach was employed. Clinical and methodological heterogeneity were appraised qualitatively; statistical heterogeneity was assessed with I^2 and τ^2. Where pooling was justified, a random-effects model (restricted maximum likelihood) was used; sensitivity analyses (leave-one-out, risk-of-bias strata) were pre-specified if pooling was feasible. If not feasible, results stayed in narrative form.

Quality control and risk of bias assessment

Reviewers were blinded to each other's initial screening and data extraction decisions to reduce bias. Risk of bias was assessed at the study level using standardized tools selected according to study design. Randomized controlled trials (including secondary and subgroup analyses of randomized trials) were evaluated with RoB 2. Non-randomized studies of interventions (e.g., real-world cohorts, single-arm clinical series, non-randomized comparative analyses) were assessed with ROBINS-I. Studies in which the exposure was not assigned by investigators (e.g., pregnancy exposure studies based on registries/claims, spontaneous reporting databases) were assessed

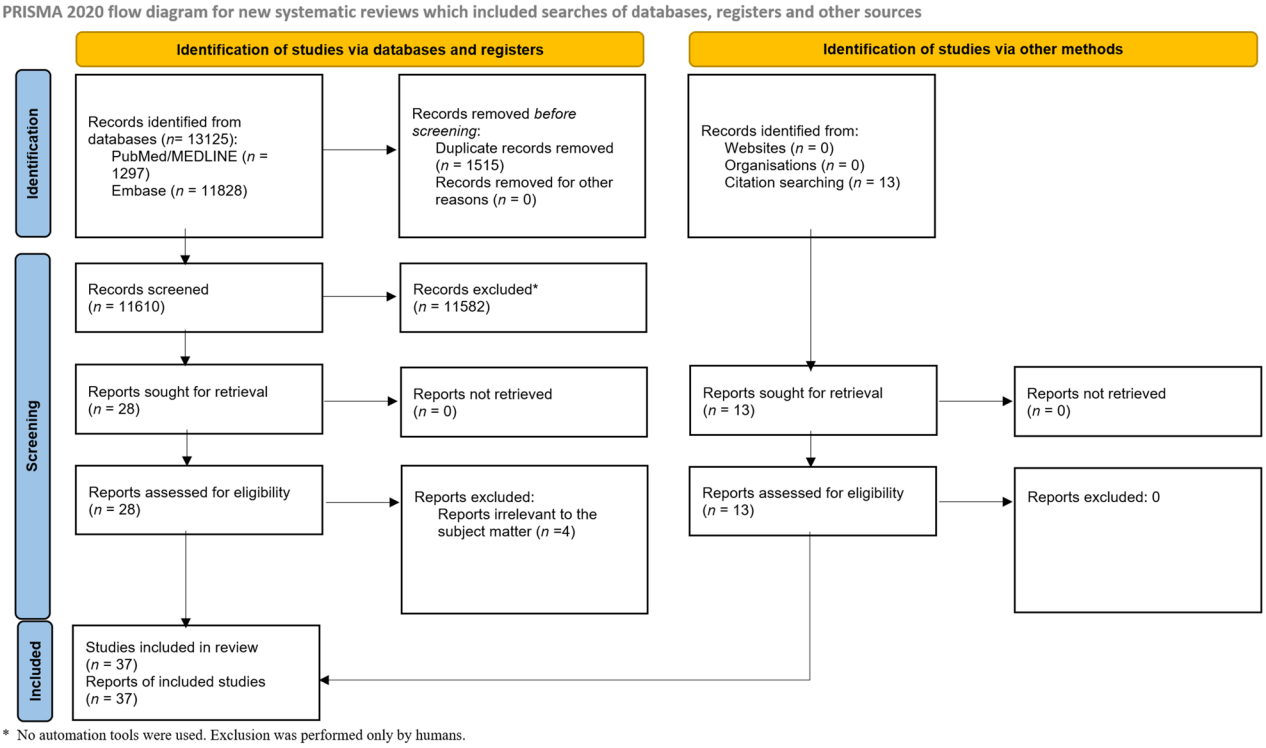

Fig. 1 Study flowchart diagram

with ROBINS-E. For each included study, judgments were made independently across the relevant domains of the chosen tool and then summarized as an overall risk-of-bias judgment, following the standard decision rules of each framework. Full details, and relative tables, are available in the Supplementary Material.

Quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was applied independently by two reviewers to assess the certainty of evidence for each outcome relevant to the predefined PICO questions [30], with disagreements resolved by consensus. Assessments were conducted outcome-specifically, drawing on the available evidence for that outcome, based on full-text evaluation of study design, methods, results, and reported limitations. Starting certainty levels were assigned according to study design, with downgrades or upgrades applied based on predefined criteria derived from GRADE handbook recommendations and adapted for migraine studies (e.g., emphasizing subgroup imbalances in sex-specific analyses) [31]. Due to the marked heterogeneity of study designs, endpoints, populations, and the predominance of post-hoc sex-stratified analyses, as well as the overall scarcity of adequately powered data (particularly for male subgroups and pregnancy safety), the GRADE ratings were not used as the sole determinant of the final recommendations, which were formulated through a structured Delphi consensus process integrating evidence appraisal and expert clinical judgment. This approach reflects the intrinsic limitations of the evidence and the consensus-based nature of the Delphi process. Detailed Evidence Profiles, including domain-specific justifications and downgrading/upgrading rationale, are provided in the Supplementary Material for transparency.

Delphi consensus development process

It was anticipated during the planning stages of the review that the available evidence could be insufficient to support an evidence-based approach for many of the proposed PICO questions. Prior to initiating the Delphi process, all PICO questions lacking sufficient data were re-evaluated for both their relevance and the likelihood of achieving expert consensus, based on the retrieved evidence. To ensure that only the most pertinent and essential items were advanced, all authors independently rated the importance of each question using a 7-point Likert scale (1 = not important, 7 = critically important), in accordance with GRADE and COMET consensus methodology. Questions were retained for the Delphi process if ≥70% of authors assigned a rating of ≥6. [32].

The panel of experts convened for the Delphi study included four of the authors (DU, GT, AvD, MB), 9 EHF board members and 9 other experts identified through their publication record, leadership roles, and

involvement in relevant clinical or methodological guideline development. A minimum of 20 participants was targeted to ensure diversity and breadth of input, in line with published recommendations [33]. The Delphi process was managed by 3 authors (RGG, SM, MB).

The initial round of the Delphi process was open-ended, as participants were invited to provide detailed responses to each of the retained PICO questions, drawing upon their personal clinical experience and, when applicable, supporting their views with relevant evidence from the literature.

Based on these results, the Delphi management team drafted a preliminary answer to each PICO question that was presented to the panel for agreement and comments. In the second round, each panel member rated every item using a 7-point Likert scale (1 = not important, 7 = critically important). Panelists were also invited to provide qualitative comments and suggest modifications to improve item clarity and relevance. Consensus was predefined as ≥70% of panelists rating an item as 6–7 (agreement) and ≤15% rating it as 1–3 (disagreement), in accordance with established best practice reporting guidelines [34].

If most of the items did achieve the predefined consensus threshold after the first iteration, panelists were asked to revise or rewrite the proposed initial statements, providing justifications supported by evidence or clinical experience. The three members of the Delphi management team would then independently review and refined the revised statements and resolving any discrepancies by consensus.

Up to two additional rounds were allowed to achieve consensus. In each round, the full Delphi panel re-rated the finalized statements, with the management group refining wording to ensure agreement and response stability. This iterative process allowed reflection, reduced bias, and encouraged convergence of expert opinions. All Delphi rounds were conducted electronically to preserve anonymity and minimize group conformity bias. Participation was voluntary, and all experts provided informed consent.

Statistical analysis

Descriptive statistics were used to analyze Delphi ratings; for meta-analyses (if applicable), pooled effect estimates (e.g., risk ratios, mean differences) were calculated using random-effects models, with heterogeneity assessed via I^2 statistics. Subgroup analyses explored sex-specific differences where data allowed.

Ethical considerations

As a literature review and consensus process, this study did not require ethical approval. However, the panel is committed to principles of transparency, inclusivity, and scientific integrity throughout the entire process.

Results

Evidence synthesis

Part I, biological sex differences in clinical expression and risk of comorbidities

For PICOs 1 through 5, no studies identified in this systematic review reported data that directly addressed these questions. Consequently, no conclusions could be drawn based on the current evidence base, and these PICOs were considered for the Delphi process.

For PICO 6 (Table 2), only one study (the CaMeo Study) specifically examined the transition from episodic (EM) to chronic migraine (CM) by sex. This longitudinal, web-based survey followed 16,789 adults with migraine over one year, with assessments every three months. Variables compared by gender included age at onset, attack frequency and severity, aura, allodynia, depression, anxiety, healthcare use, disability, and CM transition. Although the crude 1-year CM risk was similar between sexes, men showed higher adjusted risks at 6, 9, and 12 months (HR = 1.48, 2.04, 2.04; $p < 0.05$) [35]. No studies were found comparing sex differences in medication overuse or medication overuse headache.

Evidence summary: Based on currently available evidence, including data derived from a single longitudinal study there is limited but suggestive evidence that male sex may be associated with a higher risk of progression from episodic to chronic migraine over a one-year period when controlling for relevant risk factors.

Part II, sex differences in treatment outcomes

For PICOs 7 through 10, and for PICOs 13 through 15, no studies identified in this systematic review reported data that directly addressed these questions so these PICOs were considered for the Delphi process.

For PICO 11, only two studies were identified (Table 2). The two meta-analyses on acute treatment efficacy by Porreca et al. [19] and Goadsby et al. [36] were both retained. Despite partially overlapping primary studies, the analyses differed in their statistical approaches and interpretations.

A 2024 subpopulation analysis by Porreca et al. re-examined FDA dossiers for the three approved gepants (ubrogepant, rimegepant, zavegepant), stratified by sex across five randomized, placebo-controlled trials (≈14% men). In women, gepants significantly outperformed placebo for pain freedom (mean gain = 9.5%, NNT = 11) and freedom from the most bothersome symptom (10.2%, NNT = 10). In men, pooled gains were smaller and non-significant (2.8% and 3.2%, NNTs = 36 and 32). Treatment effects were consistently higher in women ($p = 0.00024$) and had no comparable benefit in men. Part of the

Table 2 Retrieved studies (per PICO)

Authors	Year	Study Design	Outcome measures	Main Findings
PICO 6. In people with migraine, how does the risk of developing chronic migraine, medication overuse and/or medication overuse headache differ between individuals of female and male sex?				
Scher A *et al* [35]	2019	Longitudinal Cross-sectional survey	CM onset in females vs males	Crude 1-year CM incidence was similar in women and men; however, by interval, HRs for men vs women were 1.48 at 6 months ($p = 0.047$) and 2.04 at 9 and 12 months (each $p < 0.05$)
PICO 11: In adults with migraine, does the effectiveness of acute attack treatment differ between females and males?				
Porreca et al. [19]	2024	Pooled data from 5 RCTs	Ubrogepant, Zavegepant, Rimegepant	Gepants have clear acute efficacy in women; current evidence base is insufficient to establish comparable benefit in men
Goadsby et al. [36]	2025	Pooled data from 4 RCTs	Ubrogepant	No significant sex interaction for any outcome
PICO 12: In adults with migraine, does the effectiveness of preventive treatment differ between females and males?				
Maassen Van Den Brink et al. [37]	2021	Phase 3b RCT post-hoc analysis	Fremanezumab	No significant sex interaction for any outcome
Ornello et al. [38]	2021	Pooled real-world data analysis from 16 headache centres	Erenumab	No significant sex interaction for any outcome
Martin et al. [39]	2022	Post hoc analysis of two pooled phase 3 RCTs	Eptinezumab	No significant sex interaction for any outcome
Ashina et al. [40]	2023	Phase 3b RCT post-hoc analysis	Eptinezumab	No significant sex interaction for any outcome
Porreca et al. [19]	2024	Pooled data from 11 RCTs	Erenumab, Galcanezumab, Fremanezumab, Eptinezumab, Atogepant	Anti CGRP mAbs slightly more effective in women than in men with EM; no differences between patients with CM or patients treated with atogepant were found.
Goadsby et al. [36]	2025	Pooled data from 4 RCTs	Atogepant	No significant sex interaction for any outcome
PICO 16: In individuals with menstrual-related migraine, which treatments are effective for managing acute migraine attacks?				
Khoo et al. [41]	2024	Meta-analysis of RCTs on acute menstrual migraine treatment	Rizatriptan Sumatriptan Sumatriptan + Naproxen Zolmitriptan Naratriptan Almotriptan Frovatriptan Lasmiditan Acetaminophen 250 mg + caffeine 85 mg + acetylsalicylic acid 250 mg	All analyzed treatments were significantly more effective than placebo at both 2 and 24 h. Sumatriptan was the most effective first-line treatment for acute menstrual migraine (MM) pain relief at 2 hours and 24 hours. Lasmiditan can be used as an acute treatment option for MM in the short term. Both 2 and 24 h after use, frovatriptan was less effective than all other triptans.
PICO 17: In individuals with menstrual-related migraine, which short-term treatments are effective for preventing migraine attacks?				
Khoo et al. [41]	2024	Meta-analysis of RCTs on MM prevention treatment	Naratriptan Zolmitriptan Frovatriptan Naproxen	Frovatriptan 2.5 mg twice daily was the most effective short-term prophylaxis treatment. Naratriptan, zolmitriptan, and naproxen also show some benefit in short-term treatment to prevent migraine attacks.
Cetin et al. [42]	2025	Prospective open study	Greater occipital nerve (GON) blockade with a standard dose of 20 mg lidocaine hydrochloride at each injection site	GON blockade may be an effective option for short-term and long-term prophylaxis in the treatment of MM, reducing the frequency and severity of headaches and improving quality of life and psychological state.
PICO 18. In individuals with menstrual-related migraine, which prophylactic treatments are effective at preventing migraine attacks?				

Table 2 (continued)

Authors	Year	Study Design	Outcome measures	Main Findings
Khoo et al. [41]	2024	Meta-analysis of RCTs	Galcanezumab (120 mg SC monthly, 6 months) Erenumab (70 mg SC monthly, 6 months)	Galcanezumab and erenumab (OR: 2.349 and OR: 2.195, respectively) are effective in achieving ≥ 50% reduction from baseline in monthly migraine days.
Silvestro et al. [43]	2021	Non-randomized open-label real-world study	Galcanezumab, Fremanezumab, Erenumab (70 mg, 140 mg)	A reduction in median menstrual migraine attack frequency (from 5 to 2 days per month), pain intensity (from 8/10 to 6/10), and attack duration (from 24 to 8 hours) ($p < 0.001$) was observed after CGRP monoclonal antibody treatments.
Allais et al. [44]	2011	Post-hoc subgroup analysis of RCT	Topiramate 50–200 mg/day, 6 months	Topiramate reduced the frequency of perimenstrual migraine in women with MRM, including migraine with and without aura, and regardless of combined oral contraceptive use. The reduction in migraine frequency with topiramate treatment was similar for perimenstrual period (PMP) and non-PMP migraine.
Verhagen IE et al. [45]	2023	Post-hoc analysis of a single-arm, real-world cohort	Erenumab, Fremanezumab	Anti-CGRP mAbs produced similar reductions in perimenstrual and non-perimenstrual migraine days (OR for treatment 0.44, 95% CI 0.38–0.51; no treatment×menstrual-window interaction, $p = 0.726$) supporting prophylactic use in menstrual migraine.
Burke et al. [46]	2002	Randomized, double-blind, placebo-controlled RCT	Phytoestrogen combination (soy isoflavones 60 mg, dong quai 100 mg, black cohosh 50 mg daily) for 24 weeks	The phytoestrogen combination effectively reduced ($p < 0.01$) the average number of menstrual migraine attacks, the frequency of any migraine attacks, the average headache severity score, and the use of triptans and pain medications per person compared with placebo
Authors	**Year**	**Study design**	**Exposure**	**Main finding**
PICO 20A: In pregnant women with migraine, which acute treatments are safe for managing migraine?				
Olesen et al. [47]	2000	Prescription–birth registry linkage	Sumatriptan	Higher odds of preterm birth and low birthweight;
Källén et al. [48]	2001	Medical Birth Registry cohort	Triptans (predominantly sumatriptan)	No increase in congenital malformations; small, non-significant elevations in preterm/low birthweight.
Nezvalová-Henriksen et al. [49]	2010	Prospective birth cohort (MoBa) + registry linkage	Triptans (≈50% sumatriptan; also rizatriptan, zolmitriptan, eletriptan)	Modest ↑ uterine atony and postpartum blood loss with later use.
Källén et al. [50]	2011	National registers (antenatal interview + prescribed drug data)	Drugs for migraine including triptans	Any malformation OR 0.95 (95% CI 0.80–1.12); 1st-trimester sumatriptan risk near unity.
Nezvalová-Henriksen et al. [51]	2013	Prescription–birth registry linkage	Triptans redeemed in pregnancy (sumatriptan, rizatriptan, eletriptan, zolmitriptan; smaller: almotriptan, naratriptan)	No malformation association; 2nd-trimester redemption associated with postpartum hemorrhage (aOR ~1.57).
Wood et al. [52]	2016	Prospective cohort (MoBa)	Sumatriptan, rizatriptan, zolmitriptan, eletriptan, naratriptan, almotriptan	Externalizing behavior aRR ~1.36 vs migraine/no-triptan; absolute risks low (~12% vs 9%).
Harris et al. [53]	2018	Prospective cohort (MoBa)	Sumatriptan, rizatriptan, zolmitriptan, eletriptan, naratriptan, almotriptan	No adverse neurodevelopment at 5 years; higher sociability scores vs untreated migraine in pregnancy.
Spielmann et al. [54]	2018	Prospective observational cohort	Sumatriptan, rizatriptan, zolmitriptan, eletriptan, naratriptan, almotriptan	No ↑ major defects (aOR 0.84, 95% CI 0.4–1.9) or preterm (1.01, 0.7–1.5); miscarriage HR 1.20 (0.9–1.7).
Harris et al. [55]	2022	Prospective cohort (MoBa)	Sumatriptan, rizatriptan, zolmitriptan, eletriptan, naratriptan, almotriptan	No association with ADHD diagnosis (wHR 1.16, 95% CI 0.78–1.74) or symptoms.
Bérard et al. [56]	2021	Population-based cohort	Sumatriptan, rizatriptan, zolmitriptan, eletriptan, almotriptan, naratriptan	↑ spontaneous abortion (aOR 1.63, 95% CI 1.34–1.98); no overall ↑ major malformations; GI defects aRR 2.04 (1.01–4.11).
Marchenko et al. [57]	2015	Meta-analysis	Sumatriptan, rizatriptan, zolmitriptan, eletriptan, naratriptan, frovatriptan	No ↑ major malformations vs migraine controls (OR 0.84, 95% CI 0.61–1.16); vs healthy controls OR 1.18 (0.97–1.44); ↑ SAB vs healthy controls (OR 3.54, 95% CI 2.24–5.59).

Table 2 (continued)

Authors	Year	Study Design	Outcome measures	Main Findings
Dudman et al. [58]	2022	Systematic review & meta-analyses	Triptans (predominantly sumatriptan data available)	Major malformations aOR 1.07 (0.83–1.39); BW < 2500 g aOR 1.18 (0.94–1.48); GA < 37 wks aOR 1.49 (0.37–6.08).
Bérard et al. [59]	2024	Retrospective cohort (claims-based)	Sumatriptan, rizatriptan, zolmitriptan, eletriptan, almotriptan, naratriptan)	No association with major malformations (aRR 0.83, 95% CI 0.58–1.19), prematurity (0.94, 0.80–1.10), LBW (1.39, 0.85–2.27), or SAB (aOR 0.88, 0.63–1.24).
PICO 20B: In pregnant women with migraine, which preventive treatments are safe for managing migraine?				
Noseda et al. [60]	2021	WHO VigiBase pharmacovigilance disproportionality	erenumab, galcanezumab, fremanezumab	Ninety-four pregnancy/lactation reports; 23 spontaneous abortions, 3 preterm births, 2 birth defects; no disproportionality vs full database; signal versus triptans disappeared after excluding confounded reports.
Noseda et al. [61]	2023	WHO VigiBase update	erenumab, galcanezumab, fremanezumab, eptinezumab	Two hundred eighty-six pregnancy-related reports; 63 spontaneous abortions, 8 prematurity, 23 neonatal outcomes including 9 birth defects; no disproportionality vs full database, 2018-onward database, or triptans.
Noseda et al. [62]	2024	WHO VigiBase comparison vs triptans	erenumab, galcanezumab, fremanezumab, eptinezumab, ubrogepant, rimegepant, atogepant	Four hundred sixty-seven pregnancy exposures overall (386 mAbs; 76 gepants; 5 both); no increased reporting vs triptans overall, for pregnancy outcomes, or foetal/neonatal outcomes.
Wong et al. [63]	2020	Prospective real-world cohort (single tertiary headache clinic)	OnabotulinumtoxinA (PREEMPT paradigm)	Among 45 exposed pregnancies (32 continued during gestation; 13 stopped), there was 1 miscarriage in the continued group and no congenital malformations; all other deliveries were full-term with normal birthweights.
Brin et al. [64]	2023	Retrospective postmarketing safety database review (29-year update)	OnabotulinumtoxinA (Allergan Global Safety Database; indications included migraine/headache ~30%)	Across 195 prospective pregnancies (197 fetuses), live-birth defect prevalence was 2.6% overall and 0.7% for major defects; rates were consistent with background; most exposures were preconception/first trimester.
Smirnoff et al. [65]	2025	Retrospective cohort + phone survey	Bilateral greater occipital nerve blocks (lidocaine 1%; rarely bupivacaine 0.5%)	Thirty pregnancies; no significant pregnancy or fetal complications reported; preterm births 4/30 (13%); one twin loss (3%); minor neonatal anomalies 1/31 (3%) each (cryptorchidism, craniosynostosis, murmur); median VAS reduced 8→2 at 2 h; acute-medication days reduced 5.5→3.0/month; minor bleeding 2/30 (7%).

Authors	Year	Study design	Exposure	Milk transfer metrics	Infant/Clinical
PICO 21: In breastfeeding women with migraine, which treatments are safe for managing migraine?					
Wojnar-Horton et al. [66]	1996	Lactation PK ($n = 5$)	Sumatriptan 6 mg SC (single dose)	Mean milk:plasma ratio 4.9 (95% CI 4.1–5.7); total recovered in milk 14.4 µg over 8 h (0.24% of 6 mg); RID 3.5% of maternal wt-adjusted dose; ~0.49% after assuming 14% infant oral F.	Single-dose, infrequent use; authors suggest optional pump-and-discard for ~8 h to further minimize infant exposure.

Table 2 (continued)

Authors	Year	Study Design	Outcome measures	Main Findings	
Amundsen et al. [67]	2021	Lactation PK ($n=19$; 22 milk sets)	Triptans: sumatriptan (8), rizatriptan (5), zolmitriptan (4), eletriptan (3), almotriptan (1), naratriptan (1)	Mean RIDs (range): eletriptan 0.6% (0.3–0.8), sumatriptan 0.7% (0.2–1.8), rizatriptan 0.9% (0.3–1.4), almotriptan 1.8%, zolmitriptan 2.1% (0.7–5.3), naratriptan 5.0%.	All mean RIDs < 10% threshold; authors caution naratriptan may be less preferred in the neonatal period; no infant adverse effects reported.
Baker et al. [68]	2022	Lactation PK (Phase 1; $n=12$)	Rimegepant 75 mg PO (single dose)	Mean RID 0.51% (SD 0.14); mean infant dose 0.005 mg/kg/day; maternal wt-normalized dose 1.04 mg/kg/day.	RID < 1% suggests compatibility with breastfeeding after single-dose use; no infant adverse events reported in study.

Authors	Year	Study design	Exposure	Main finding
PICO 23: In pregnant women with migraine, which treatments are effective for preventing migraine attacks?				
Smirnoff *et al* [65]	2025	Retrospective cohort + phone survey ($n=21$)	Bilateral GON blocks (lidocaine 1%; rarely bupivacaine 0.5%)	Median pain score reduced from 8.0 (IQR 7.0–8.0) pre-procedure to 2.0 (IQR 0.0–4.0) at 2 hours ($p<0.001$). Median monthly acute-medication days fell from 5.5 (IQR 0.8–12.0) to 3.0 (IQR 0.0–5.0) ($p=0.002$).
PICO 24: In post-menopausal women with migraine, which treatments are effective for managing migraine?				
Guerzoni et al. [69]	2023	Prospective real-world cohort (12 months) on 233 patients	Anti-CGRP mAbs: erenumab, galcanezumab, fremanezumab	Comparable reduction of monthly headache days in post-menopausal vs childbearing-age women
Argyriou et al. [70]	2024	Post-hoc analysis of a prospective registry (24 weeks) on 171 patients	Fremanezumab	Both pre- and post-menopausal women improved significantly in monthly headache days, disability, and quality of life; no between-group differences

attenuation in men reflected a higher placebo response, but even where placebo rates were similar the active–placebo difference remained modest [19].

A 2025 secondary analysis by Goadsby et al. pooled four ubrogepant RCTs (10–14% men). Two phase 3 trials showed similar efficacy between sexes: pain freedom at 2 h was 19.4% (men) vs 21.1% (women); most-bothersome-symptom relief was 35.1% vs 39.0%, with no significant sex interactions. Phase 2b and prodrome-phase trials showed comparable patterns. Odds of avoiding moderate-to-severe headache within 24 h of prodromal dosing were 1.79 (men) vs 2.16 (women) [36].

Evidence Summary: Based on post-hoc and pooled analyses of FDA-submitted phase 2 and phase 3 trials of gepants (ubrogepant, rimegepant, and zavegepant) for the acute treatment of migraine, there is no definitive evidence of a clinically meaningful sex-based difference in overall treatment effectiveness. Ubrogepant had no statistically significant sex–treatment interaction while rimegepant and zavegepant show clear and consistent efficacy in women, while evidence in men remains limited and inconclusive. Interpretation is constrained by the post-hoc nature of subgroup analyses and the underrepresentation of male participants, stressing the need for prospectively powered studies with balanced sex representation.

For PICO 12, six studies were retrieved (Table 2).

A sex-stratified post-hoc analysis of the phase 3b FOCUS trial evaluated fremanezumab in adults with episodic or CM who had failed two to four previous preventives. Among 837 participants (16% men), fremanezumab reduced monthly migraine days (MMDs) by 4.1–4.6 days in men and 3.6–3.9 in women, versus minimal change with placebo. Treatment-by-sex interaction was nonsignificant ($p = 0.36$). Headache days, ≥50% responder rates, acute treatment days, and MIDAS scores improved similarly in both sexes, though HIT-6 scores reached significance only in women [37].

A pooled post-hoc analysis of PROMISE-1 (EM) and PROMISE-2 (CM) [39] assessed eptinezumab (1737 participants; 13% men). Both 100 mg and 300 mg doses produced nearly identical benefits in men and women, with responder rates around 55–60% on active drug vs ~40% on placebo. Confidence intervals overlapped, and no sex interaction was detected, suggesting comparable efficacy. The DELIVER trial ($n = 890$; 10% men) confirmed similar reductions in MMDs across sexes (−5.0 vs −4.5 to −5.2; $p = 0.51$ [40]).

A 2024 FDA dossier review reanalyzed all CGRP-targeting preventives (mAbs and atogepant), separating results by sex across 11 randomized, placebo-controlled trials. In EM, treatment effects were consistent but somewhat smaller in men (mean reduction −0.5 to −1.0 vs −1.3 to −2.1 days; pooled male-to-female ratio 0.55). In CM, efficacy was nearly equivalent between sexes (ratio 0.90). Interestingly, atogepant showed slightly larger mean effects in men, though sample sizes were small. Overall, anti-CGRP mAbs were unequivocally effective in women and effective, though slightly less so, in men with EM, with similar benefit once migraine became chronic [19].

A 2025 pooled analysis [36] of four atogepant trials (10–14% men) found no sex-related efficacy differences. In EM, the 60 mg dose yielded a placebo-adjusted MMD reduction of −1.95 in men vs −1.13 in women; in CM, reductions were −2.26 vs −2.46 days, respectively. Results were consistent across doses and trials.

Finally, a real-world pooled analysis [38] of erenumab outcomes across 16 headache centers ($n = 1{,}410$; 18% men) found no significant sex differences in responder rates or efficacy measures. MHDs fell by 6.9 days in men and 7.9 in women; MMDs by 7.1 vs 7.7; and HIT-6 disability scores by 8.4 vs 9.1 (all $p > 0.05$). Adjusted analyses confirmed that sex did not influence treatment response.

Overall, across RCTs and real-world data, anti-CGRP agents (mAbs and gepants) demonstrate robust efficacy in both sexes. Slightly smaller effects in men with episodic migraine were noted. However, once migraine becomes chronic, efficacy appears equivalent between men and women.

Evidence Summary: Based on evidence from multiple phase 3 and 3b randomized, placebo-controlled trials and pooled post-hoc sex-stratified analyses, preventive therapies targeting the CGRP pathway, including mAbs (fremanezumab, eptinezumab, erenumab, galcanezumab) and atogepant, demonstrate broadly similar reductions in migraine burden in adult females and males, with no evidence of a clinically meaningful treatment-by-sex interaction in either episodic or chronic migraine. Interpretation remains provisional due to the underrepresentation of men and the post-hoc nature of subgroup analyses; however, current evidence do not support sex-specific differences in preventive efficacy.

Part III, fertility and reproduction-specific management Issues

For PICOs 19 and 22 no studies identified in this systematic review reported data that directly addressed these questions so they were considered for the Delphi Process.

For PICO 16, only one study was identified (Table 2).

A meta-analysis by Khoo et al. [41] of 26 RCTs ($n = 8{,}926$) on menstrual migraine (MM) compared the efficacy of acute treatments using SUCRA rankings and odds ratios. All drugs outperformed placebo for pain relief at 2 and 24 hours. At 2 hours, sumatriptan ranked highest (SUCRA = 0.963), followed by zolmitriptan, rizatriptan, and lasmiditan; at 24 hours, sumatriptan and lasmiditan remained top-ranked (0.868 and 0.755). Forest plots confirmed sumatriptan 100 mg as most effective

at 2 h (OR 4.62, 95% CI 3.23–6.60), followed by almotriptan 12.5 mg and zolmitriptan 2.5 mg. At 24 h, lasmiditan showed the strongest effect (OR 4.81, 95% CI 1.02–22.68).

In summary, all acute agents - triptans, lasmiditan, and AAC (acetaminophen + caffeine + aspirin) - were superior to placebo. Sumatriptan 100 mg is the most effective for 2-hour pain freedom, while lasmiditan offers sustained 24-hour benefit. Frovatriptan showed weaker early efficacy, and rizatriptan had reduced effect at 24 hours

Evidence Summary: High-quality evidence from a comprehensive meta-analysis of 26 randomized controlled trials involving 8,926 patients with menstrual-related migraine demonstrates that all evaluated acute therapies, including triptans (rizatriptan, sumatriptan, zolmitriptan, naratriptan, almotriptan, frovatriptan), sumatriptan plus naproxen, lasmiditan, and an acetaminophen–acetylsalicylic acid–caffeine combination, are significantly more effective than placebo for pain freedom and pain relief at both 2 and 24 hours. Sumatriptan showed the most consistent efficacy across included trials and emerged as the highest-ranked acute treatment. Lasmiditan represents an effective alternative, especially when triptans are contraindicated or not tolerated. Frovatriptan appears less effective for acute relief but may retain a role in short-term perimenstrual prophylaxis.

For PICO 17, two studies were retrieved (Table 2).

A meta-analysis by Khoo et al. [41] found strong evidence supporting short-term perimenstrual preventive therapy for MM. Overall efficacy was significant (OR 2.25, 95% CI 1.90–2.66), with frovatriptan 2.5 mg twice daily the most effective (OR 3.01), followed by once-daily frovatriptan and naratriptan 1 mg twice daily. For ≥ 50% reduction in MMDs, zolmitriptan 2.5 mg twice daily ranked highest, with naratriptan providing comparable though slightly weaker benefit. Naproxen 550 mg twice daily also reduced monthly headache days (−1.4 MMDs).

A 2025 prospective study [42] of GON blockade with lidocaine in 33 women who had used at least two prophylactic medications without benefit showed significant, sustained reductions in pain and disability scores over six months, though sample size was small.

Evidence Summary: High-quality evidence, including a comprehensive meta-analysis and a prospective interventional study, supports the use of short-term perimenstrual preventive therapy with triptans to significantly reduce the risk of menstrual migraine attacks in individuals with menstrual-related migraine. Among available regimens, frovatriptan 2.5 mg twice daily, administered for six days starting two days before menses, demonstrates the greatest preventive efficacy among evaluated regimes. Other triptan regimens, including frovatriptan 2.5 mg once daily, naratriptan 1 mg twice daily, and zolmitriptan 2.5 mg twice daily, also provide significant but less robust benefit. Naproxen 550 mg twice daily for 14 days per month shows moderate efficacy and represents a reasonable non-triptan alternative. Preliminary evidence suggests that GON blockade with lidocaine may offer benefit however, current data are limited and larger controlled studies are required.

For PICO 18, five studies were identified (Table 2).

A meta-analysis by Khoo et al. [41] found both galcanezumab and erenumab effective for menstrual-related migraine (MRM) prevention; ≥50% responder rates favored galcanezumab (OR 2.35) and erenumab (OR 2.20), with corresponding mean MMD reductions of −2.36 and −2.10.

In a real-world cohort ($n = 40$) [43] treated with CGRP mAbs (fremanezumab, galcanezumab, erenumab), perimenstrual attack frequency, duration, intensity, and MMDs all improved significantly (median MMDs 19→5, $p < 0.001$). Over half achieved > 50% reduction in MM days.

A post-hoc PROMPT analysis [44] showed topiramate (50–200 mg/day, 6 months) reduced monthly migraine frequency by ~47% (MMD −3.1), with similar benefit during and outside perimenstrual periods, independent of oral contraceptive use.

Verhagen et al. [45] reported that erenumab and fremanezumab reduced MMDs by 31% over six months (−4.4 days/month) with similar efficacy during and outside the menstrual window.

A placebo-controlled RCT [46] found soy-based phytoestrogens significantly reduced MRM attack frequency, severity, and medication use versus placebo ($p < 0.01$).

Evidence Summary: Evidence from randomized controlled trials, meta-analyses, and real-world cohort studies supports the use of CGRP-targeted mAbs (including galcanezumab, erenumab, and fremanezumab) as effective preventive therapies for menstrual-related migraine, with consistent reductions in attack frequency, duration, and severity observed both during and outside the perimenstrual window. Among non-CGRP preventive options, topiramate showed moderate efficacy, although we need to consider its reproductive safety. A soy-based phytoestrogen has shown preliminary benefit in reducing menstrual migraine frequency and severity.

For PICO 20, 19 studies were retrieved, subdivided between acute(A) and preventive(B) exposures (Table 2).

For PICO 20A, thirteen studies were identified (Table 2). The two meta-analyses on triptan safety in pregnancy by Marchenko et al. [57] and Dudman et al. [58] were both retained. Despite partially overlapping primary studies they employ different comparators, use different statistical methods, and cover different time periods, providing complementary perspectives on the same safety question.

The meta-analysis by Marchenko et al. [57], found no increased risk of major congenital malformations when comparing triptan-exposed pregnancies to migraine controls (OR 0.84, 95% CI 0.61–1.16) or to healthy controls (OR 1.18, 0.97–1.44).

Spontaneous abortion rates were higher in the triptan-exposed group versus healthy controls (OR 3.54, 95% CI 2.24–5.59), though not versus migraine controls. A subsequent systematic review and meta-analysis by Dudman et al. [58] confirmed no significant increase in major malformations (aOR 1.07, 0.83–1.39), low birthweight (aOR 1.18, 0.94–1.48), or prematurity (aOR 1.49, 0.37–6.08) when comparing triptan users to the general population.

Beyond the outcomes captured by these pooled analyses, several individual studies reported additional clinically relevant data and were therefore retained in the evidence table. Olesen et al. [47] and Källén et al. [48] reported on low birthweight as a separate outcome, with increased odds in the former (OR 3.0) but non-significant elevations in the latter. Nezvalová-Henriksen et al. [49], within the Norwegian Mother and Child Cohort (MoBa), found no elevated risk of major malformations but reported that second- or third-trimester exposure was weakly associated with postpartum haemorrhage (adjusted OR 1.3; 95% CI 1.1–1.5) and uterine atony (adjusted OR 1.4; 95% CI 1.1–1.8). Spielmann et al. [54] documented similar rates of major birth defects (OR 0.84, 95% CI 0.4–1.9), spontaneous abortion (HR 1.20, 0.9–1.7), and preterm delivery (OR 1.01, 0.7–1.5), with analyses stratified by gestational timing of exposure.

Neurodevelopmental follow-up studies in MoBa by Wood et al. [52] and Harris et al. [53, 55]—outcomes entirely outside the scope of the available meta-analyses—found no evidence of adverse behavioural or cognitive outcomes, and no increased risk of ADHD through 3, 5 and 10 years of follow-up.

A few analyses, such as Bérard et al. [56], reported higher odds of spontaneous abortion (OR 1.63, 95% CI 1.34–1.98) and gastrointestinal malformations (OR 2.04, 95% CI 1.01–4.11), but these findings were not replicated. A large claims-based study by Bérard et al. [59] found no association with major malformations (aRR 0.83, 95% CI 0.58–1.19), prematurity (0.94, 0.80–1.10), low birthweight (1.39, 0.85–2.27), or spontaneous abortion (aOR 0.88, 0.63–1.24).

Overall, current evidence supports that triptans, particularly sumatriptan, do not appear to increase the risk of congenital or developmental abnormalities, and may be considered for use in pregnancy when clinically indicated.

Evidence Summary: Based on the current body of evidence, including multiple large registry studies, cohort analyses, and meta-analyses, sumatriptan and other triptans appear to be safe for acute migraine treatment during pregnancy, particularly when exposure occurs in the first trimester. Across studies totaling several thousand exposed pregnancies, triptan use has not been associated with an increased risk of major congenital malformations, no significant increase in overall risks of stillbirth, prematurity, or low birth weight compared with either migraine-affected or general-population controls.

Single studies of mid-to-late pregnancy exposure show modestly increased risks of uterine atony and postpartum hemorrhage in registry-based cohorts, but the risk was low, and it is unclear if migraine disease severity was accounted for. Long-term neurodevelopmental follow-ups show no adverse effects at five years and no increased ADHD risk, with small absolute differences in externalizing behaviors at age three.

Overall, triptans in pregnancy can be considered when clinically necessary, with awareness near delivery.

For PICO 20B, six studies were identified (Table 2).

Noseda et al. [61] analyzed WHO VigiBase reports up to 2019 (94 exposures) and 2021 (286 exposures) to CGRP mAbs, identifying spontaneous abortion as the most frequent outcome but finding no consistent disproportionality signal versus the full database or triptans after adjustment. An extension through May 2023 [62] captured 467 pregnancy exposures to CGRP antagonists (mostly mAbs but also including gepants), with no increased reporting compared with triptans and lower reporting odds for maternal, fetal, and neonatal outcomes.

For onabotulinumtoxinA, Wong et al. [63] followed 45 exposed pregnancies, including 32 who continued treatment during pregnancy, with one miscarriage and no congenital abnormalities with a mean follow-up of 3.5 years. Larger safety database analyses (Brin et al. [64], 913 reported pregnancies; 195 prospective) showed defect rates comparable to background, with a major-defect prevalence of 0.7% among live births.

Smirnoff et al. [65] reported outcomes in 30 pregnancies exposed to GON blocks, 18% in the first trimester, 54% in the second, and 28% in the third; with lidocaine 1% (98%) or bupivacaine 0.5% (2%) noting some obstetric complications and mostly minor neonatal findings, without a clear safety signal.

Evidence Summary: Based on currently available evidence that includes limited observational registry data, retrospective cohort studies, and pharmacovigilance analyses, there is no clear evidence of teratogenic or major obstetric risk associated with the use of onabotulinumtoxinA for CM and GON blocks used as preventive interventions for migraine during pregnancy.

CGRP mAbs and gepants on > 450 pregnancy exposures show no emerging safety signal in postmarketing data regarding spontaneous abortion, congenital anomalies, or adverse neonatal outcomes relative to either

triptan comparators, but due to unsystematic nature of these data sources, evidence remains insufficient to support routine use during pregnancy.

For PICO 21, three lactation studies were identified (Table 2).

Wojnar-Horton et al. [66] studied five lactating women given subcutaneous sumatriptan 6 mg. Although milk concentrations exceeded plasma (milk:plasma AUC ratio 4.9), the absolute infant exposure was very low (0.24% of the maternal dose); the effective infant dose was < 0.5% after accounting for oral bioavailability. Given the short maternal half-life (~2 hours) and episodic dosing, the authors concluded continued breastfeeding is unlikely to pose significant risk. Amundsen et al. [67] analysed breast-milk transfer of six triptans in nineteen breastfeeding women. Mean relative infant doses were low for all agents ranging from 0.6–2.1% for most triptans except naratriptan (eletriptan 0.6%, 0.3–0.8; $n = 3$, sumatriptan 0.7%, 0.2–1.8; $n = 8$, rizatriptan 0.9% 0.3–1.4; $n = 5$, almotriptan 1.8%, single subject, zolmitriptan 2.1%, 0.7–5.3; $n = 4$, and naratriptan 5.0% single subject), while remaining below the 10% compatibility threshold. No infant adverse events were reported.

Baker et al. [68] conducted a single-dose pharmacokinetic study of rimegepant in twelve lactating women and found minimal milk transfer (mean relative infant dose 0.51%, SD 0.14) well below standard safety thresholds for breastfeeding compatibility, with no reported infant adverse events.

Evidence Summary: Based on currently available pharmacokinetic and lactation data, sumatriptan and other triptans with short half-lives (e.g., eletriptan, rizatriptan, zolmitriptan) demonstrate minimal transfer (well below the conventional 10% safety threshold) into human breast milk and are considered compatible with breastfeeding when used at therapeutic doses for acute migraine management. Naratriptan, given its higher RID and prolonged half-life, may be less preferred during the immediate neonatal period, though still within acceptable safety margins.

Available data of a single small open-label study indicate that rimegepant transfer into breast milk is negligible, supporting its compatibility with lactation.

For PICO 23, one retrospective cohort study was identified (Table 2).

Smirnoff et al. [65] evaluated bilateral GON blocks in pregnant women with migraine in an uncontrolled and open study. Median pain scores decreased from 8.0 pre-procedure to 2.0 at 2 hours post-block ($p < 0.001$). Monthly days of acute medication use also declined from 5.5 to 3.0 ($p = 0.002$). Analyses were not stratified by trimester.

Evidence Summary: Based on a single small uncontrolled retrospective cohort study, bilateral GON blocks appear effective in reducing acute pain and reliance on acute medications during pregnancy, with no procedure-related maternal or fetal safety concerns identified. Given limited preventive options in pregnancy, GON blockade showed acute pain reduction and decreased acute medication use, with no identified safety concerns.

For PICO 24, two real-world studies were identified (Table 2).

Guerzoni et al. [69] prospectively compared menopausal and reproductive-age women treated with anti-CGRP mAbs (mostly erenumab and galcanezumab) over 12 months. Monthly headache days, acute medication use, and disability scores (HIT-6, MIDAS) improved similarly in both groups, with no sustained between-group differences. Outcomes were comparable across natural versus surgical menopause and between erenumab and galcanezumab; lower baseline analgesic use predicted excellent response (>75% reduction in monthly headache days) at 12 months ($p = 0.03$).

Argyriou et al. [70] conducted a post-hoc analysis of a prospective registry of women treated with fremanezumab for 24 weeks. Significant improvements in headache days, disability, and quality of life were observed in both pre- and post-menopausal women, with no differences between groups.

Evidence Summary: In two studies, anti-CGRP mAbs demonstrated robust, sustained effectiveness in post-menopausal women, aligning closely with responses in younger, reproductive-age patients, indicating that menopausal status does not modify treatment response and should not influence clinical decision-making.

Delphi consensus results

PICOs 1–5, 7–10, 13–15, and 19–23 were considered for the Delphi process because the systematic review did not identify studies directly addressing these questions or because available evidence was insufficient to fully answer them. These PICOs therefore underwent the predefined retention and iteration process (Table 3). PICOs 1–4 and 20–23 were retained, whereas PICOs 5, 7–10, and 13–15 were excluded from the Delphi process. PICO 19 achieved a rating ≥ 6 by 67% of panelists; although slightly below the pre-specified 70% threshold, the Delphi management group deemed the topic sufficiently relevant and approved its inclusion.

All invited experts participated in Round 1 ($n = 22$), which was conducted in an open format; input from all panelists was therefore considered in drafting the initial responses to each PICO question. Panel retention remained high across subsequent rounds, with participation rates of 86% ($n = 19$) in Round 2, 72% ($n = 16$) in Round 3, and 86% ($n = 19$) in Round 4. Consensus was achieved for all proposed PICOs, with 72% reaching agreement by the third round; PICOs 4, 21B, and 23

Table 3 Retention and iteration Delphi process for each PICO

PICO N	Agreement level, result			
	To include in Delphi	Round 2 version	Round 3 version	Round 4 version
1	79%, Included	68%, no consensus	79%, consensus	
2	79%, Included	58%, no consensus	79%, consensus	
3	82%, Included	62%, no consensus	82%, consensus	
4	83%, Included	47%, no consensus	64%, no consensus	84%, consensus
5	42%, Not Included			
7	33%, Not Included			
8	42%, Not Included			
9	33%, Not Included			
10	33%, Not Included			
13	25%, Not Included			
14	59%, Not Included			
15	58%, Not Included			
19	67%, Included	63%, no consensus	71%, consensus	
20 A	83%, Included	63%, no consensus	71%, consensus	
20 B	83%, Included	37%, no consensus	86%, consensus	
21 A	75%, Included	58%, no consensus	79%, consensus	
21 B	75%, Included	47%, no consensus	50%, no consensus	74%, consensus
22	75%, Included	42%, no consensus	71%, consensus	
23	75%, Included	39%, no consensus	64%, no consensus	84%, consensus

required a fourth round to achieve consensus. Final Delphi statements for all included PICOs are presented in Table 4, with corresponding agreement levels and intermediate formulations provided in the Supplementary Material (Supp Table 2).

Puberty and Adolescence (PICO 1): Before puberty, migraine prevalence is similar in boys and girls [71, 72]. During early adolescence, prevalence rises in females, who may also experience higher attack frequency or duration [73–75]. Childhood-onset migraine is more likely to persist in females [76], with peak incidence for migraine with and without aura occurring 5–6 and 4–6 years later, respectively, in females than in males [77]. Hormonal changes, particularly estrogen fluctuations [4, 78], as well as psychosocial and environmental factors [79], likely contribute to these differences.

Reproductive Years (PICO 2): Females show higher prevalence and greater clinical burden than males [3], with menstrual-related attacks being longer, more disabling, and less responsive to treatment [80, 81]. Hormonal fluctuations appear to modulate migraine susceptibility, as estrogen withdrawal is associated with increased risk of attacks, particularly migraine without aura, whereas high-estrogen states and exogenous estrogen exposure have been linked to migraine with aura [82–84]. Experimental data support biological plausibility for sex-specific mechanisms, while evidence for hormonally driven modulation of migraine in males remains limited; observations in transgender individuals receiving hormone therapy further support a role of sex hormones in migraine expression [11, 22, 85–87]

End of Reproductive Years (PICO 3): The transition out of the reproductive phase can be associated with sex-specific differences [77, 88, 89] as migraine may worsen during perimenopause due to hormonal fluctuations [90, 91], and some women show increased frequency, severity, duration, and reduced predictability, particularly in women with menstrual-related migraine [92–95]. Observational data further suggest that migraine expression may become more variable, with new-onset or phenotypic changes [89, 92–95]. After menopause, at persistently low oestrogen concentrations, many women report improvement, though attacks may persist, especially with aura [92, 93, 96]. Male migraine tends to remain stable with gradual age-related decrease [78].

Hormonal treatments (PICO 4): In females, estrogen fluctuations modulate migraine. Combined hormonal contraceptives can worsen migraine with aura, while continuous or progestin-only regimens may reduce perimenstrual attacks [97, 98]. Hormone replacement therapy effects are variable, with low-dose transdermal estrogen preferred [92, 99, 100]. Data in males are limited; testosterone therapy may improve migraine in some cases, including gender-affirming treatment [22, 87, 101].

Safety in fertility and pregnancy (PICO 19 and 20): Safety of migraine treatment depends on pregnancy planning and contraceptive reliability. In addition to triptans, acetaminophen is the safest acute option, while NSAIDs

Table 4 Retained PICO questions and final consensus answers

PICO Question	Final Delphi statement
PICO 1: In children and adolescents with migraine, how does entering puberty influence the clinical expression of migraine in females compared to males?	The influence of puberty on the clinical expression of migraine differs between females and males, likely attributed to sex-specific hormonal changes. With the onset of puberty, migraine becomes more prevalent in females, who often experience greater migraine-related burden, including higher attack frequency, pain intensity and longer attack duration, compared to males, contributing to a clear female predominance during and after puberty.
PICO 2: In individuals of reproductive age with migraine, does being in the reproductive period lead to different clinical expressions of migraine in females compared to males?	During the reproductive years, clinically meaningful sex-based differences in migraine expression are evident. Females exhibit higher migraine prevalence and tend to have more frequent, prolonged, and severe attacks, with greater associated disability. Menstrual migraine represents a female-specific subtype in which perimenstrual attacks are often more disabling and less responsive to acute treatment than non-perimenstrual attacks. Estrogen fluctuations seem to modulate migraine susceptibility in some individuals. Estrogen decline is often associated with increased risk of attacks, particularly of migraine without aura. High-estrogen states (e.g., pregnancy, exogenous estrogen exposure) have been linked to increased occurrence of migraine with aura attacks, although causal relationships in both situations have not been definitively established. In males, migraine patterns remain comparatively stable, with no clear evidence of hormone-driven variability.
PICO 3: In individuals with migraine reaching the end of the reproductive phase, how does this transition affect clinical migraine expression in females compared to males?	At the end of the reproductive phase, migraine expression diverges significantly between females and males. In females, the perimenopausal transition, characterized by high and fluctuating estrogen levels, frequently leads to worsening migraine, with increased frequency, severity, and reduced predictability. After menopause, when hormone levels stabilize at consistently low estrogen concentrations, most women experience improvement in migraine, although attacks may persist, including in those with migraine with aura. Males do not undergo comparable hormonal transitions; migraine in males tends to show a gradual decline or remain stable with advancing age, without the marked variability observed in females.
PICO 4. In people with migraine, how do hormonal treatments influence migraine expression in females compared to males?	Combined hormonal contraceptives (CHCs) may worsen or precipitate migraine with aura and can trigger attacks during the hormone-free interval. In contrast, continuous CHC regimens and progestin-only formulations may help prevent menstrually related migraine. Hormone replacement therapy (HRT) has variable effects on migraine, with low-dose continuous transdermal estrogen being preferable to other formulations. In males, evidence regarding the effects of hormonal treatments on migraine is very limited, and current data are insufficient to draw conclusions about testosterone therapy or other hormonal interventions.
PICO 19: In women of childbearing potential with migraine, which treatments are safe for managing migraine?	In women of childbearing potential (WOCBP), the safety of migraine pharmacological treatment depends on pregnancy planning and the use of effective contraception. With reliable contraception, all standard acute and preventive migraine therapies may be considered. In WOCBP without contraception or those planning pregnancy acetaminophen/paracetamol is the safest option for attack treatment, while triptans, particularly sumatriptan, are acceptable for severe attacks. NSAIDs may be used cautiously. In WOCBP without contraception or those planning pregnancy preferred options for migraine prevention include propranolol, low-dose amitriptyline, and onabotulinumtoxinA (for chronic migraine). Supplements such as magnesium and riboflavin may be offered, acknowledging limited evidence. Preventive treatment with valproate, topiramate, ACE inhibitors and ARBs, ergot derivatives and venlafaxine should be avoided because of teratogenic or fetal risk; CGRP mAbs and gepants should be discontinued in sufficient time to completely eliminate the drug before conception, which is likely months in mAbs due to their long half-life and days in gepants. Shared decision-making with neurologists and obstetrics is recommended when planning pregnancy.
PICO 20A: In pregnant women with migraine, which acute treatments (excluding triptans) are safe for managing migraine attacks?	In pregnant women with migraine, acetaminophen/paracetamol is the safest and preferred first-line acute treatment across all trimesters. Safe adjuncts include antiemetics such as metoclopramide and prochlorperazine, as well as the antihistamine diphenhydramine for associated symptoms or sleep support. Non-steroidal anti-inflammatory drugs (e.g. ibuprofen, naproxen) may be used in the second trimester, for short courses and with caution, and should be avoided in the first and third trimesters. Greater occipital nerve blocks, short courses of oral corticosteroids preferably after the first trimester, and intravenous magnesium are considered safe for severe or refractory attacks. Drugs to avoid include gepants, butalbital, opioids due to the risk of dependence and neonatal withdrawal and ergot derivatives. Multidisciplinary management with neurology and obstetrics is recommended for refractory or severe attacks, and non-pharmacological management should be prioritized whenever feasible.

Table 4 (continued)

PICO Question	Final Delphi statement
PICO 20B: In pregnant women with migraine, which prophylactic treatments (excluding onabotulinium toxin and mAbs targeting the CGRP pathway) are safe for managing uncontrolled migraine?	In pregnant women with uncontrolled migraine, no prophylactic drug is entirely risk-free, but select options may be used when non-pharmacological measures are insufficient always considering the risk-benefit.
	Beta-blockers and low-dose amitriptyline may be used with caution, avoiding beta-blockers late in pregnancy due to risks of fetal growth restriction and bradycardia. Calcium channel blockers are considered safe, although effectiveness is uncertain.
	Greater occipital nerve blocks with lidocaine can be considered in selected cases. Supplements such as magnesium may be used, acknowledging limited safety data.
	Drugs with known teratogenicity or insufficient safety data, including valproate,
	topiramate, ACE inhibitors, ARBs, venlafaxine and gepants should be avoided.
	Any pharmacologic prophylaxis should involve neurology and obstetrics management with close maternal and fetal monitoring.
PICO 21A. In breastfeeding women with migraine, which acute treatments (excluding triptans) are safe for managing migraine attacks?	In breastfeeding women with migraine, acetaminophen/paracetamol and NSAIDs, particularly ibuprofen, naproxen, and diclofenac, are considered first-line and generally safe options for acute treatment. Anti-emetics such as domperidone and prochlorperazine may be used for associated nausea, although safety data for metoclopramide are limited. Magnesium and small amounts of caffeine can be considered as adjuncts.
	Emerging data suggest that gepants have minimal transfer into breast milk, but evidence remains limited; their use is generally not recommended pending further safety data.
	Aspirin (acetylsalicylic acid), butalbital-containing drugs, ergot derivatives, and opioids should be avoided due to potential risks to the infant.
	Clinical management should prioritize minimizing infant exposure and involve multidisciplinary input when needed
PICO 21B. In breastfeeding women with migraine, which preventive treatments are safe for managing migraine?	In breastfeeding women with migraine, beta-blockers, particularly propranolol and metoprolol, and tricyclic antidepressants, such as amitriptyline or nortriptyline, are generally considered first-line preventive options due to their established safety and low infant exposure. OnabotulinumtoxinA may also be used for chronic migraine, although data are limited. Peripheral nerve blocks are low-risk and compatible with breastfeeding.
	Topiramate, valproate, and candesartan require careful consideration in difficult-to-treat cases due to potential risks to the infant and limited human safety data. Evidence on the use of CGRP mAbs or gepants during lactation is emerging and although data does not suggest increased risk if used after the newbord period, their use is still not recommended until further safety data become available.
	Preventive therapy should be prescribed at the lowest effective dose and infant monitoring is advised.
PICO 22. In pregnant women with migraine, which treatments (excluding occipital nerve blocks with lidocaine) are efficient for managing migraine attacks?	Evidence on efficacy comes largely from studies in non-pregnant populations, but available data supports acetaminophen/paracetamol being preferred for mild attacks, while sumatriptan is most effective for moderate to severe attacks. NSAIDs can be used in the second trimester. Metoclopramide, prochlorperazine, and ondansetron are effective options for treating nausea and may contribute to overall attack relief.
	Intravenous magnesium may be considered in refractory cases, although evidence is limited.
	Treatment should be individualized with input from neurology and obstetrics.
PICO 23. In pregnant women with migraine, which prophylactic treatments (excluding occipital nerve blocks with lidocaine) are efficient for managing migraine attacks?	In pregnant women with migraine, evidence on preventive efficacy is limited, and treatment decisions rely mainly on extrapolation from non-pregnant populations together with pregnancy-specific safety considerations. Prophylaxis is generally reserved for those with frequent, severe, or disabling attacks that do not respond to non-pharmacological measures, as migraine often improves during pregnancy.
	Beta-blockers, particularly propranolol, are an established preventive option and should be used at the lowest effective dose due to potential fetal growth risks. Low-dose amitriptyline may also be considered as an alternative.
	OnabotulinumtoxinA is effective for chronic migraine, pregnancy data suggest minimal systemic absorption and low fetal risk, making its use reasonable after careful risk–benefit assessment.
	Fetal monitoring and multidisciplinary collaboration with neurology and obstetrics are recommended when pharmacologic prophylaxis is required.

may be used avoiding the late stages of pregnancy due to fetal risks, having most data derived from established obstetric pharmacology [102]. Antiemetics such as metoclopramide, prochlorperazine, and diphenhydramine are acceptable adjuncts for symptom control, supported by extensive clinical experience and routine obstetric use [102, 103]. Magnesium, GON blocks and short courses of corticosteroids are safe rescue options [65, 102, 104]. Gepants, ergot derivatives, butalbital-containing compounds, and opioids are not recommended due to insufficient data or potential fetal harm [102, 103]. Overall, treatment should prioritize minimal pharmacological exposure while preserving maternal function, with escalation guided by trimester-specific safety considerations and shared decision-making.

For preventive treatment, none is completely risk-free. In addition to onabotulinumtoxinA for CM, beta-blockers, low-dose amitriptyline have the best safety profiles, but caution of beta-blockers use late in pregnancy is due to possible fetal growth restriction and neonatal bradycardia [63, 64, 102]. Calcium channel blockers and GON blocks are also considered low-risk alternatives;

magnesium and riboflavin are frequently used in clinical practice, but safety evidence is limited [65, 102]. Teratogenic drugs (valproate, topiramate) and drugs with potential fetal risks (ACE inhibitors, ARBs, ergot derivatives, venlafaxine) should be avoided, and CGRP mAbs or gepants require discontinuation prior to conception [105]

Efficacy in Pregnancy (PICO 22 and 23): The evidence on efficacy of acute and preventive migraine treatments in pregnancy mainly extrapolates findings from non-pregnant adults. For attack management acetaminophen remains the preferred first-line option for mild attacks, with modest efficacy [102, 106]; NSAIDs can be effective, but may be used in the second trimester only [107] while sumatriptan has a strong support [108]. Metoclopramide, prochlorperazine and ondansetron improve nausea and can contribute to overall symptom relief [102, 109]; the evidence for magnesium efficacy remains limited [104]. For prevention, the use of onabotulinumtoxinA for CM [63], and beta-blockers or low-dose amitriptyline [102, 106] are preferred due to safety and show acceptable efficacy during pregnancy.

Overall, treatment decisions require balancing efficacy, teratogenic risk, and pregnancy intention, with shared decision-making recommended. With effective contraception, standard treatments may be considered, while in those planning pregnancy or without contraception, safer options such as acetaminophen, selected triptans, and selected preventives are preferred [102].

Lactation (PICO 21): Paracetamol and ibuprofen are first-line acute treatments; naproxen and diclofenac may be used cautiously due to longer half-lives [102]. Metoclopramide or domperidone may be used for nausea monitoring possible effects on maternal sedation and milk production [102]. Evidence supporting safety and efficacy of magnesium and caffeine in breastfeeding is limited [102]. Preliminary data suggest low milk transfer of gepants, yet evidence remains insufficient to recommend its use during lactation [68]. Drugs to be avoided include aspirin, opioids, ergot derivatives and butalbital-containing combinations, due to recognised risks such as Reye's syndrome, neonatal respiratory depression or sedation [102].

Preventive options with established safety include beta-blockers and tricyclic antidepressants [102]; onabotulinumtoxinA has limited direct lactation data, yet transfer into breast milk is thought to be minimal [110]. Magnesium, and riboflavin have limited breastfeeding-specific safety data are limited [102]. Topiramate may be acceptable and valproate shows low milk transfer, but both are generally avoided because of broader safety concerns and risk of future pregnancy exposure [102]. Data in lactation for anti-CGRP mAbs and gepants remain insufficient for recommendation, despite low theoretical infant exposure [92, 101].

Discussion and further directions

This review was structured into three sections. Part I examined biological sex differences in the clinical expression and comorbidities of migraine across different life stages. Specifically, it explored how the onset of puberty influences migraine characteristics in females compared to males during childhood and adolescence; whether being in the reproductive phase leads to sex-related differences in migraine presentation among adults; and how the transition out of the reproductive period affects migraine expression in women relative to men. Additionally, this section considered how hormonal treatments may modulate migraine differently across sexes, and whether females and males differ in their risk of developing migraine-related complications, CM, or medication-overuse headache.

Except for data on the risk of developing CM [35], evidence addressing these questions was inexistent. We found a suggestion of a higher transition rate from episodic to CM occurring in males, yet evidence remains insufficient to support sex-specific preventive or management strategies. Notably, a previous population-based longitudinal study assessing transition to "transformed migraine" suggested that the relationship between sex and migraine chronification may be medication-dependent, with sex potentially modifying the association between certain acute drug classes and the risk of transition [111]. Therefore, further studies using contemporary diagnostic criteria and evaluating sex impact as the primary outcome are needed before drawing firm conclusions on sex-specific risks and preventive recommendations.

The evidence to answer the remaining questions is scarce and limited to descriptive studies, so our conclusions relied on expert consensus due to the scarcity of robust, sex-stratified data.

Consensus was achieved that hormonal transitions across the lifespan play a central role in shaping sex differences in migraine expression. With puberty onset, migraine becomes more prevalent and severe in females, leading to the clear female predominance that persists through adulthood. During the reproductive years, women experience higher attack frequency, greater intensity, and increased disability, particularly in association with menstrual migraine, where perimenstrual attacks are often more disabling and less responsive to treatment [3, 75]. These differences appear closely linked to estrogen fluctuations, though causal relationships remain uncertain [4, 78]. Toward the end of the reproductive phase, perimenopause often exacerbates migraine, while stabilization after menopause usually

Table 5 Summary of therapeutic recommendations

		Evidence Synthesis	Experts' Opinion
ACUTE TREATMENT	Differences according to sex	No difference: rimegepant and zavegepnat; ubrogepant	
	Menstrual Migraine	EFFICACY Sumatriptan most effective, all triptans and lasmiditan	
	WOCP without contraception and pregnant	SAFETY: triptans	SAFETY: Acetaminophen/paracetamol, metoclopramide, prochlorperazine, diphenhydramine, NSAIDS (only 2nd trimester), GON blocks, short courses of steroids (2nd and 3rd trimesters), Mg EFFICACY Acetaminophen for mild attacks, sumatriptan for moderate to severe attacks, antiemetics and Magnesium
	Breastfeeding women	SAFETY Sumatriptan and short-acting triptans	SAFETY Acetaminophen, NSAIDs, domperidone, prochlorperazine, Magnesium, caffeine
PREVENTIVE TREATMENT	Differences according to sex	No difference: Anti-CGRP mAbs and atogepant	
	Menstrual Migraine	EFFICACY Short time prevention: Frovatriptan Long term prevention: Topiramate, Erenumab, galcanezumab	
	WOCP without contraception and pregnant	SAFETY GON Blocks, onabotulinumtoxinA EFFICACY GON BLOCKs	SAFETY Betablockers (1st and 2nd trimesters), amitriptyline, Mg, calcium channel blockers, EFFICACY Propranolol, amitriptyline, onabotulinumtoxinA
	Breastfeeding women		SAFETY beta-blockers, tricyclic antidepressants, OnabotulinumtoxinA, GON blocks
	Postmenopausal women	anti-CGRP mAbs	

brings improvement. In contrast, males show more stable migraine patterns throughout life, lacking comparable hormonal variability. Hormonal treatments further reflect this sex-specific influence as combined hormonal contraceptives may worsen migraine with aura, while continuous or progestin-only regimens can reduce menstrual-related attacks; among hormone replacement therapies, low-dose continuous transdermal estrogen appears to have less impact on migraine expression. Evidence on hormonal treatments in males, however, remains sparse and inconclusive [112]. Given the increasing popularity of testosterone supplements, investigating the impact of testosterone containing medication on migraine expression should be investigated.

The second major topic addressed in this review concerned sex differences in treatment outcomes. This section aimed to examine whether biological sex or gender-related hormonal influences modify the effectiveness or safety of migraine therapies across the lifespan, including puberty, adulthood, and older age, as well as in individuals undergoing long-term gender-affirming hormonal therapy. The intent was to determine whether the efficacy and safety of both acute and preventive migraine treatments differ between females and males, or between transgender and cisgender individuals.

Systematic data were available only for adults, specifically addressing if the effectiveness of anti-CGRP in the acute and preventive treatment of migraine differs between sexes. While evidence supports, with low to moderate quality, that the preventive efficacy of CGRP mAbs and oral CGRP receptor antagonists is comparable between male and female adults, for acute migraine treatment evidence remains low for rimegepant and zavegepant in men, while ubrogepant seems to have comparable efficacy between sexes [19, 36, 37, 39, 40]. Nevertheless, these findings do not support sex-based modifications in treatment choice, dosage, or expected outcomes (Table 5). However, given the differences between men and women on the CGRP receptor level, it is important that sex differences in drug responsiveness is given attention in future research.

The persistent underrepresentation of men in migraine clinical trials, constituting only 10–18% of participants in most trials, limits the certainty of these conclusions. Whether this imbalance reflects the higher disease burden in women or differences in diagnostic accuracy or

healthcare-seeking behaviour remains unclear [113]; however, it evidently introduces potential bias in efficacy data. Encouragingly, recent clinical trials have begun to report sex-stratified outcomes, which are important steps toward closing this gap. Yet, there remains a clear need for deliberate inclusion strategies for men in future research.

All other questions within this topic, addressing potential sex and gender differences in treatment outcomes for other drug classes, as well as during puberty, aging, and in transgender individuals, lacked sufficient or relevant evidence. The scarcity of data was such that none of these questions was voted for inclusion in the Delphi process, as given the current state of knowledge, it was considered that no meaningful conclusions or consensus statements could be established. This highlights an urgent need for research in this area, in particular to confirm potential therapeutic equivalence between sexes and to elucidate biological or pharmacokinetic factors that may influence treatment response over the lifespan.

The third topic addressed fertility and reproduction-specific management issues, including menstrual-related migraine and treatment safety during pregnancy, lactation, and menopause (Table 5). In WOCP, the expert panel concluded that the safety of pharmacological migraine therapy depends on the use of effective contraception, so that all acute and preventive migraine treatments may be considered when reliable contraception is in place. However, use of valproate and topiramate should be in line with European pregnancy prevention programs for these drugs [114, 115]. In the absence of contraception, management should include the same precautions applied to women planning or with known or suspected pregnancy.

The topic that had the most available data, allowing for low to moderate quality, evidence-based recommendations was regarding the efficacy of acute, short-term preventive, and long-term preventive strategies for menstrual-related migraine. Evidence supports the use of triptans, lasmiditan, erenumab, and galcanezumab for these indications [41, 43, 45], as well as the use of erenumab, galcanezumab, and fremanezumab for preventive treatment in postmenopausal women [69, 70].

Ample evidence also exists regarding the safety of triptans, particularly in terms of risk of congenital malformations. There are also some reproductive safety data regarding GON blocks, onabotulinumtoxinA in managing migraine in WOCP without effective contraception and planning/during pregnancy, as well as a suggestion of efficacy for GON blocks [57, 63–65]. However, these data are primarily derived from small case series or pharmacovigilance safety databases, thus the confidence in these findings remains low. However, due to the local administration of GON blocks and onabotulinumtoxinA with limited systematic effects expected, reproductive safety is presumed and these treatments can be recommended if treatment is needed close to or during pregnancy.

For lactating women, safety evidence is primarily based on studies assessing drug transfer into breast milk and, in some cases, registry data on infant outcomes, and it supports the use of triptans as an acute treatment during breastfeeding [66, 67].

All other recommendations on this topic are based on expert consensus, reflecting real-world experience, observational data, or the extrapolation of findings from non-migraine populations treated with the same agents. For example, reproductive safety data for antihypertensive treatments are derived from use of these drugs for cardiovascular disorders [116], supporting the existence of a substantial knowledge gap in this area. Safety in WOCP remains particularly critical, as this population represents the largest therapeutic gap. Preventive treatments are often discontinued when pregnancy is planned due to uncertainty regarding safety, leading to prolonged periods (sometimes months or years) without adequate migraine control in women. Consequently, clinicians face the dilemma of either maintaining suboptimal management or exposing patients to potential risks. These aspects support the need for further investigation in migraine-specific cohorts, including studies addressing the effects of treatments on fertility and reproductive outcomes in both women, but also men of childbearing potential.

For WOCP and pregnant patients, acetaminophen triptans and NSAIDs (in the 2nd trimester) may be used while metoclopramide, prochlorperazine, diphenhydramine are considered relatively safe adjuncts. Propranolol, amitriptyline, and onabotulinumtoxinA are preferred for preventive therapy while lidocaine GON blocks can be used either as acute or preventive treatment [102].

This review has inherent methodological limitations due to the nature of the available studies. While PRISMA ensured comprehensive, reproducible searches and minimized selection bias, it highlighted the scarcity of high-quality RCTs, particularly in vulnerable populations such as pregnant or lactating women, leading to reliance on registries, pharmacovigilance data, and small pharmacokinetic cohorts. Applying the GRADE framework provided a structured assessment of evidence quality but revealed that most data are observational, post-hoc, or indirect, resulting in predominantly low or very low certainty ratings. Although consistent real-world patterns are reassuring, the lack of primary outcomes explicitly designed to assess sex, menopausal, or pregnancy-specific differences limits causal inference and calls for cautious interpretation in clinical practice.

In conclusion, this review highlights major gaps in sex- and gender-specific migraine research. While hormonal

transitions clearly shape migraine patterns in women, robust evidence on sex-related differences in CM risk or treatment response is lacking. Men remain markedly underrepresented in trials, limiting confidence in efficacy data. Moderate evidence supports triptans, lasmiditan, and CGRP-targeted agents for menstrual-related migraine, and suggests acceptable safety of triptans, onabotulinumtoxinA, and occipital nerve blocks in WOCP without effective contraception, pregnancy and lactation. Most recommendations, however, rely on observational data or expert consensus. Future research should prioritize sex- and gender-stratified analyses, include diverse populations, and incorporate life-stage and reproductive-specific endpoints as primary outcomes in RCTs where feasible, to strengthen evidence quality and advance personalized migraine care.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-026-02350-x.

Supplementary Material 1

Acknowledgements

We would like to express our sincere gratitude to the following experts who generously contributed their time, expertise, and insights as members of the Delphi panel (listed in alphabetical order): Addie Peretz, Anne MacGregor, Annelies Van Dycke, Betul Baykan, Bianca Rafaelli, Cheryl Carcel, Christina Deligianni, Christian Lampl, Derya Uluduz, Erling Tronvik, Faisal Amin, Gabriele Merki-Feld, Gisela Terwindt, Britt van der Arend, Hedvig Nordeng, Jan Versijpt, Kjersti G. Vetvik, Kristina Ryliskiene, Margarita Sanchez del Rio, Marte-Helene Bjork, Phil Holland, Rebecca Burch and Uwe Reuter. Their expert contributions significantly enriched the quality and robustness of our work. We are deeply thankful for their collaboration.

Author contributions

Raquel Gil-Gouveia, Antoinette MaassenVanDenBrink, Derya Uluduz, Christina Deligianni, Christian Lampl, Erling Tronvik, Faisal Amin, Jan Versijpt, Kristina Ryliskiene, Margarita Sanchez del Rio, Phil Holland and Uwe Reuter conceptualized the study, together with Simone Braca and Francesco Casillo designed the systematic review protocol. Authors Simone Braca, Francesco Casillo, Esme Ekizoglu, Stefanie Moreira and Marte-Helene Bjork conducted the literature search and data extraction. Simone Braca, Esme Ekizoglu, Francesco Casillo, Marte-Helene Bjork, Stefanie Moreira, Anna K. Szewczyk, Annelies Van Dycke, Derya Uluduz, Gianluca Coppola and Raquel Gil-Gouveia reviewed the abstracts and full-text articles. Simone Braca and Francesco Casillo summarized and analyzed the systematic review data and applied the GRADE system. Raquel Gil-Gouveia, Stefanie Moreira and Marte-Helene Bjork managed the consensus methodology, including the Delphi panel coordination and data synthesis. The manuscript structure and outline was drafted by Raquel Gil-Gouveia, who wrote the introduction and discussion. The methods section was written by Raquel Gil-Gouveia, Simone Braca and Francesco Casillo while the results section included contributions from Esme Ekizoglu, Gisela Terwindt, Marte-Helene Bjork, Stefanie Moreira, Anna K. Szewczyk, Annelies Van Dycke and Raquel Gil-Gouveia. All authors were included in all discussions, all critically reviewed the manuscript for intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

Funding

Publication of this study was supported by European Headache Federation.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Protocol registration

This review protocol was registered in the PROSPERO database (registration number: CRD420251058438).

Independence statement

The authors had full access to all data and take full responsibility for the integrity and accuracy of the analysis.

Competing interests

Simone Braca reports, unrelated to this work, over the last 36 months, personal compensation from Eli Lilly for oral presentations. Esme Ekizoglu received honoraria for lectures, presentations from Pfizer and Neutec. Francesco Casillo received honoraria for consulting activities from Abbvie. Marte-Helene Bjork is supported by public and competitive research funding sources, including the Research Council of Norway (NorHead Centre for Clinical Treatment Research, grant 328615) and the TrondMohn Foundation (SAFE ASM, grant TMF2024TMT03. She reports advisory board honoraria and/or speaking honoraria from Pfizer, Jazz Pharmaceuticals, Angelini Pharma, AbbVie, Lundbeck, Organon, and Eisai. Her institution (University of Bergen and Haukeland University Hospital) and research group (BergenBrain) have received funding from valproate marketing authorization holders forpost-marketing drug safety studies, and from Lundbeck for an industry-financed phase IV study of eptinezumab, all unrelated to the current work. Stefanie Moreira has nothing to disclose. Anna K. Szewczyk has nothing to disclose. Annelies Van Dycke received honoraria for participation on advisory/scientific boards and/or given lectures for Abbvie, Allergan, Angelini Pharma, Lilly, Lundbeck, Neuraxpharm, Novartis, Organon, Pfizer and Teva. Derya Uluduz is employed by İstanbul university Cerrahpaşa school of medicine neurology department and is a consultant for Abbvie and Pfizer. Gianluca Coppola serves as Associate Editor of The Journal of Headache and Pain, Cephalalgia, Cephalalgia Reports, Frontiers in Neurology (Neurotechnology section), BMC Neurology (Pain section), Frontiers in Human Neuroscience (Brain Imaging and Stimulation section), Headache and Pain Research, Confinia Cephalalgica. He has received honoraria as a moderator from AbbVie, Pfizer, and Eli-Lilly, has received consulting fees from AbbVie, Eli-Lilly, and Pfizer, and has been the PI in trials sponsored byPfizer and AbbVie. He has received research grants from AbbVie. Christina Deligianni has received travel grants and honoraria from AstraZeneca, Merck & Co, Pfizer and Teva Pharmaceuticals and research grants from the International Headache Society and the Hellenic Neurology Society. Christian Lampl has received consulting fees and honoraria for lectures/ presentations from AbbVie/Allergan, Eli Lilly, Lundbeck, Novartis, Pfizer, and Teva. CL participated in clinical trials as the principal investigator for Eli Lilly. Erling Tronvik has received personal fees for lectures/advisory boards: Novartis, Eli Lilly, Abbvie, TEVA, Roche, Lundbeck, Pfizer, Biogen, Organon. Consultant for and owner of stocks and IP in Man & Science. Stocks and IP in Nordic BrainTech. Stocks in Keimon Medical. Non-personal research grants from several sources, including Norwegian Research Council, KlinBeForsk, EU. Commissioned research (non-personal): Lundbeck. Faisal Amin has received personal fees for lecturing and/or participation in advisory boards from AbbVie, Eli Lilly, Lundbeck, Novartis, Pfizer, and Teva Pharmaceuticals; and research grants from the Lundbeck Foundation. Jan Versijpt received personal fees and non-financial support from Pfizer, Lilly, and Teva; personal fees from Novartis and Lundbeck; and grants and non-financial support from Allergan and AbbVie. Kristina Ryliskiene has received personal fees for lectures/advisory boards: Novartis, Abbvie, TEVA, Lundbeck, Pfizer, Viatris, Berlin Chemie. Margarita Sanchez del Rio reports personal fees as Speaker from Teva, Pfizer, Eli Lilly, Lundbeck and Organon. Phil Holland reports honoraria for educational and advisory purposes from Allergan, Novartis, and Teva as well as research funding from Eli Lilly and Company, Amgen, and Cellgene/Bristol Myers Squibb. Gisela Terwindt reports consultancy support from AbbVie, Lilly, Lundbeck, Novartis, Organon, Pfizer, Teva, and independent support from the European Community, Dutch Heart Foundation, Dutch Research Council, Dutch Brain Foundation, Dioraphte, and the Clayco foundation. Uwe Reuter has received institutional fees from Amgen, Abbvie, Lilly, Lundbeck, Novartis, Pfizer, Medscape, SandTeva, and research funding from Novartis. Antoinette MaassenVanDenBrink reports honoraria for advisory board and/or lectures from Allergan/Abbvie,Amgen/Novartis, Eli Lilly, Organo, Pfizer, as well as research grants from Manistee, Pfizer, Satsuma, Teva and Tonix. She received independent research support from the European Community and Dutch Research Council as well as the Netherlands Organisation for Health Research

and Development. Raquel Gil-Gouveia reports honoraria for consultant and/or advisory boards from Allergan/ Abbvie, Astra Zeneca,Almirall, Bial, Biogen, Bristol-Myers Squibb, CMBE, FLOAT, Lilly, Lundbeck, Merk, Novartis, Novo Nordisk, Organon, Pfizer, Roche, Sanofi, Tecnifar, and Teva; research funding from Fundação Ciência Tecnologia (Project 29675,MigN2Treat, 02/SAICT/2017); Learning-Health, Luz Saúde (LiON, Luz Innovation on Neurosciences); Novartis-Sociedade Portuguesa de Cefaleias; Bolsa –Projecto Centro de Investigação Interdisciplinar em Saúde, and UCP.

Author details
[1]Department of Neuroscience, Reproductive Sciences and Odontostomatology, University of Naples "Federico II", Naples, Italy
[2]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino ICOT, Latina, Italy
[3]Department of Neurology, Unidade Local de Saúde Braga, Braga, Portugal
[4]Department of Neurology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey
[5]Department of Clinical Medicine, University of Bergen, Bergen, Norway
[6]Department of Neurology, Haukeland University Hospital, Bergen, Norway
[7]NorHead, Norwegian Headache Research Centre; NTNU, Norwegian University of Science and Technology, Trondheim, Norway
[8]Department of Neurology, Medical University of Lublin, Lublin, Poland
[9]Department of Neurology, General Hospital Sint-Jan Brugge, Brugge, Belgium
[10]Neurology Department, İstanbul Atlas University, Istanbul, Turkey
[11]First Department of Neurology, Aeginition Hospital, Medical School National and Kapodistrian, University of Athens, Athens, Greece
[12]Neurology Department, Athens Naval Hospital, Athens, Greece
[13]Department of Neurology, Krankenhaus Barmherzige Brüder, Linz, Austria
[14]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway
[15]Department of Neurology, Copenhagen University Hospital - Amager and Hvidovre Hospital, Hvidovre, Denmark
[16]Department of Neurology, Universitair Ziekenhuis Brussel, Brussels, Belgium
[17]Neuroprotection and Neuromodulation Research Group, Center for Neurosciences, Vrije Universiteit Brussel, Brussels, Belgium
[18]Institute of Clinical Medicine, Neurology and Neurosurgery Clinic, Vilnius University, Vilnius, Lithuania
[19]Department of Neurology, Clínica Universidad de Navarra, Calle Marquesado de Santa Marta, 1, Madrid 28027, Spain
[20]Headache Group, Wolfson Sensory Pain and Regeneration Centre, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK
[21]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands
[22]Department of Neurology, Charité Universitätsmedizin Berlin, Corporate member of Humboldt University and Freie Universität Berlin, Bonhoefferweg 3, 10117 Berlin, Germany
[23]Division of Pharmacology and Vascular Medicine, Department of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[24]Headache Center, Neurology Department, Hospital da Luz, Lisboa, Portugal
[25]Center for Interdisciplinary Research in Health, Universidade Católica Portuguesa, Lisboa, Portugal

Received: 4 February 2026 / Accepted: 23 March 2026
Published online: 17 April 2026

References

1. Husøy AK, Steiner TJ (2025) GBD 2023: over twice the health loss from headache disorders among females compared with males, and one fifth of the loss is attributable to medication overuse. J Headache Pain 26(1):227
2. Ashina M, Terwindt GM, Al-Karagholi MA, de Boer I, Lee MJ, Hay DL et al (2021) Migraine: disease characterisation, biomarkers, and precision medicine. Lancet 397(10283):1496–1504
3. Vetvik KG, MacGregor EA (2017) Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol 16(1):76–87
4. Al-Hassany L, Haas J, Piccininni M, Kurth T, Maassen Van Den Brink A, Rohmann JL (2020) Giving researchers a Headache - sex and gender differences in migraine. Front Neurol 11:549038
5. Singh S, Kopruszinski CM, Watanabe M, Dodick DW, Navratilova E, Porreca F (2024) Female-selective mechanisms promoting migraine. J Headache Pain 25(1):63
6. Maddahi A, Edvinsson JCA, Edvinsson L (2024) Sex differences in expression of CGRP family of receptors and ligands in the rat trigeminal system. J Headache Pain 25(1):193
7. Holm A, Edvinsson JCA, Krause DN, Edvinsson L (2025) RAMP1-dependent hormonal regulation of CGRP and its receptor in the trigeminal ganglion. J Headache Pain 26(1):142
8. Krivoshein G, Rivera-Mancilla E, MaassenVandenbrink A, Giniatullin R, van den Maagdenberg A (2025) Sex difference in TRPM3 channel functioning in nociceptive and vascular systems: an emerging target for migraine therapy in females? J Headache Pain 26(1):40
9. Ibrahimi K, van Oosterhout WP, van Dorp W, Danser AH, Garrelds IM, Kushner SA et al (2015) Reduced trigeminovascular cyclicity in patients with menstrually related migraine. Neurology 84(2):125–131
10. Kopruszinski CM, Lee G, Martin LK, Barber KR, Moutal A, Dodick DW et al (2024) A male-specific mechanism of meningeal nociceptor sensitization promoting migraine headache. Cephalalgia 44(9):3331024241281493
11. Eikermann-Haerter K, Dileköz E, Kudo C, Savitz SI, Waeber C, Baum MJ et al (2009) Genetic and hormonal factors modulate spreading depression and transient hemiparesis in mouse models of familial hemiplegic migraine type 1. J Clin Invest 119(1):99–109
12. Krause DN, Warfvinge K, Haanes KA, Edvinsson L (2021) Hormonal influences in migraine - interactions of oestrogen, oxytocin and CGRP. Nat Rev Neurol 17(10):621–633
13. Sandweiss AJ, Cottier KE, McIntosh MI, Dussor G, Davis TP, Vanderah TW et al (2017) 17-β-estradiol induces spreading depression and pain behavior in alert female rats. Oncotarget 8(69):114109–114122
14. van den Maagdenberg Am, Pietrobon D, Pizzorusso T, Kaja S, Broos LA, Cesetti T et al (2004) A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. Neuron 41(5):701–710
15. Sachs M, Pape HC, Speckmann EJ, Gorji A (2007) The effect of estrogen and progesterone on spreading depression in rat neocortical tissues. Neurobiol Dis 25(1):27–34
16. Brennan KC, Romero Reyes M, López Valdés HE, Arnold AP, Charles AC (2007) Reduced threshold for cortical spreading depression in female mice. Ann Neurol 61(6):603–606
17. Rivera-Mancilla E, Musterd-Bhaggoe UM, Schutter D, van den Bogaerdt A, Vincent A, Villalón CM et al (2025) Sex differences in the vasoactive effect of transient receptor potential channels: TRPM3 as a new therapeutic target for (neuro)vascular disorders. Br J Pharmacol 182(11):2503–2523
18. de Vries T, Boucherie DM, Chan KY, Rubio-Beltrán, Labastida-Ramírez, Labruijere S et al (2024) Sex differences in CGRP-induced vasodilation of human middle meningeal arteries but not human coronary arteries: implications for migraine. Cephalalgia 44(7):3331024241254088
19. Porreca F, Navratilova E, Hirman J, van den Brink AM, Lipton RB, Dodick DW (2024) Evaluation of outcomes of calcitonin gene-related peptide (CGRP)-targeting therapies for acute and preventive migraine treatment based on patient sex. Cephalalgia 44(3):3331024241238153
20. van Casteren, DS, Kurth T, Danser AHJ, Terwindt GM, MaassenVandenbrink A (2021) Sex differences in response to triptans: a systematic review and meta-analysis. Neurology 96(4):162–170
21. Trovão DinizE, Rocha Leite JB, Ribeiro Coutinho Madruga C, Maia Arca V, Macedo Cavalcanti Albuquerque JA, Sampaio Rocha-Filho PA (2025) Headache in transgender men using gender-affirming hormone therapy: a case-control study. Headache 65(8):1449–1456
22. Zavala LJ, Gil Ramirez A, Vetvik KG, Jensen RH, Hougaard A (2025) Headache in individuals undergoing hormone therapy for gender transition: a cross-sectional, observational study. Headache
23. Hranilovich JA, Kaiser EA, Pace A, Barber M, Ziplow J (2021) Headache in transgender and gender-diverse patients: a narrative review. Headache 61(7):1040–1050
24. Hranilovich JA, Millington K (2023) Headache prevalence in transgender and gender diverse youth: a single-center case-control study. Headache 63(4):517–522

25. Pace A, Barber M, Ziplow J, Hranilovich JA, Kaiser EA (2021) Gender minority stress, psychiatric comorbidities, and the experience of migraine in transgender and gender-diverse individuals: a narrative review. Curr Pain Headache Rep 25(12):82
26. Rosendale N, Guterman EL, Obedin-Maliver J, Flentje A, Capriotti MR, Lubensky ME et al (2022) Migraine, migraine disability, trauma, and discrimination in sexual and gender minority individuals. Neurology 99(14):e1549–e59
27. Martinez CI, Liktor-Busa E, Largent-Milnes TM (2024) Problems in management of medication overuse headache in transgender and gender nonconforming populations. Front Neurol 15:1320791
28. Yalinay Dikmen P, Ertas M, Kosak S, Cimentepe C, Kocoglu M, Oztosun G et al (2021) Primary headaches among gender dysphoric female-to-male individuals: a cross-sectional survey on gender transition experience. Headache 61(8):1194–1206
29. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan-a web and mobile app for systematic reviews. Syst Rev 5(1):210
30. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336(7650):924–926
31. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J et al (2011) GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64(4):401–406
32. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM et al (2014) Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 67(4):401–409
33. Gattrell WT, Logullo P, van Zuuren EJ, Price A, Hughes EL, Blazey P et al (2024) ACCORD (ACcurate COnsensus reporting document): a reporting guideline for consensus methods in biomedicine developed via a modified Delphi. PLoS Med 21(1):e1004326
34. van Zuuren, EJ, Logullo P, Price A, Fedorowicz Z, Hughes EL, Gattrell WT (2022) Existing guidance on reporting of consensus methodology: a systematic review to inform ACCORD guideline development. BMJ Open 12(9):e065154
35. Scher AI, Wang SJ, Katsarava Z, Buse DC, Fanning KM, Adams AM et al (2019) Epidemiology of migraine in men: results from the chronic migraine epidemiology and outcomes (CaMEO) study. Cephalalgia 39(2):296–305
36. Goadsby PJ, Jürgens TP, Brand-Schieber E, Nagy K, Liu Y, Boinpally R et al (2025) Efficacy of ubrogepant and atogepant in males and females with migraine: a secondary analysis of randomized clinical trials. Cephalalgia 45(2):3331024251320610
37. MaassenVandenbrink A, Terwindt GM, Cohen JM, Barash S, Campos VR, Galic M et al (2021) Impact of age and sex on the efficacy of fremanezumab in patients with difficult-to-treat migraine: results of the randomized, placebo-controlled, phase 3b FOCUS study. J Headache Pain 22(1):152
38. Ornello R, Baraldi C, Guerzoni S, Lambru G, Fuccaro M, Raffaelli B et al (2021) Gender differences in 3-month outcomes of erenumab treatment-study on efficacy and safety of treatment with erenumab in men. Front Neurol 12:774341
39. Martin V, Nagy AJ, Janelidze M, Giorgadze G, Hirman J, Cady R et al (2022) Impact of baseline characteristics on the efficacy and safety of eptinezumab in patients with migraine: subgroup analyses of PROMISE-1 and PROMISE-2. Clin Ther 44(3):389–402
40. Ashina M, Lanteri-Minet M, Ettrup A, Christoffersen CL, Josiassen MK, Phul R et al (2023) Efficacy and safety of eptinezumab for migraine prevention in patients with prior preventive treatment failures: subgroup analysis of the randomized, placebo-controlled DELIVER study. Cephalalgia 43(5):3331024231170807
41. Khoo CC, Liu CC, Lu M, Huang YC, Weng HY (2024) Acute and preventive treatment of menstrual migraine: a meta-analysis. J Headache Pain 25(1):143
42. Cetin G, Totuk O, Cetin OE, Demir S, Sahin S (2025) Evaluation of the effectiveness of greater occipital nerve blockade in menstrual migraine. BMC Neurol 25(1):62
43. Silvestro M, Orologio I, Bonavita S, Scotto di Clemente F, Fasano C, Tessitore A et al (2021) Effectiveness and safety of CGRP-mAbs in menstrual-related migraine: a real-world experience. Pain Ther 10(2):1203–1214
44. Allais G, Sanchez Del Rio M, Diener HC, Benedetto C, Pfeil J, Schäuble B et al (2011) Perimenstrual migraines and their response to preventive therapy with topiramate. Cephalalgia 31(2):152–160
45. Verhagen IE, de Vries Lentsch S, van der Arend BWH, le Cessie S, MaassenVandenbrink A, Terwindt GM (2023) Both perimenstrual and nonperimenstrual migraine days respond to anti-calcitonin gene-related peptide (receptor) antibodies. Eur J Neurol 30(7):2117–2121
46. Burke BE, Olson RD, Cusack BJ (2002) Randomized, controlled trial of phytoestrogen in the prophylactic treatment of menstrual migraine. Biomed Pharmacother 56(6):283–288
47. Olesen C, Steffensen FH, Sorensen HT, Nielsen GL, Olsen J (2000) Pregnancy outcome following prescription for sumatriptan. Headache 40(1):20–24
48. Källén B, Lygner PE (2001) Delivery outcome in women who used drugs for migraine during pregnancy with special reference to sumatriptan. Headache 41(4):351–356
49. Nezvalová-Henriksen K, Spigset O, Nordeng H (2010) Triptan exposure during pregnancy and the risk of major congenital malformations and adverse pregnancy outcomes: results from the Norwegian mother and child cohort study. Headache 50(4):563–575
50. Källén B, Nilsson E, Otterblad Olausson P (2011) Delivery outcome after maternal use of drugs for migraine: a register study in Sweden. Drug Saf 34(8):691–703
51. Nezvalová-Henriksen K, Spigset O, Nordeng H (2013) Triptan safety during pregnancy: a Norwegian population registry study. Eur J Epidemiol 28(9):759–769
52. Wood ME, Lapane K, Frazier JA, Ystrom E, Mick EO, Nordeng H (2016) Prenatal triptan exposure and Internalising and externalising behaviour Problems in 3-year-old children: results from the Norwegian mother and child cohort study. Paediatr Perinat Epidemiol 30(2):190–200
53. Harris GE, Wood M, Ystrom E, Nordeng H (2018) Prenatal triptan exposure and neurodevelopmental outcomes in 5-year-old children: follow-up from the Norwegian mother and child cohort study. Paediatr Perinat Epidemiol 32(3):247–255
54. Spielmann K, Kayser A, Beck E, Meister R, Schaefer C (2018) Pregnancy outcome after anti-migraine triptan use: a prospective observational cohort study. Cephalalgia 38(6):1081–1092
55. Harris GM, Wood M, Ystrom E, Nordeng H (2022) Association of maternal use of triptans during pregnancy with risk of attention-deficit/hyperactivity disorder in offspring. JAMA Netw Open 5(6):e2215333
56. Bérard A, Strom S, Zhao JP, Kori S, Albrecht D (2021) Dihydroergotamine and triptan use to treat migraine during pregnancy and the risk of adverse pregnancy outcomes. Sci Rep 11(1):19302
57. Marchenko A, Etwel F, Olutunfese O, Nickel C, Koren G, Nulman I (2015) Pregnancy outcome following prenatal exposure to triptan medications: a meta-analysis. Headache 55(4):490–501
58. Dudman DC, Tauqeer F, Kaur M, Ritchey ME, Li H, Lopez-Leon S (2022) A systematic review and meta-analyses on the prevalence of pregnancy outcomes in migraine treated patients: a contribution from the IMI2 ConcePTION project. J Neurol 269(2):742–749
59. Bérard A, Strom S, Albrecht D, Kori S (2024) Anti-migraine medications safety during pregnancy in the US. Front Pharmacol 15:1481378
60. Noseda R, Bedussi F, Gobbi C, Zecca C, Ceschi A (2021) Safety profile of erenumab, galcanezumab and fremanezumab in pregnancy and lactation: analysis of the WHO pharmacovigilance database. Cephalalgia 41(7):789–798
61. Noseda R, Bedussi F, Gobbi C, Ceschi A, Zecca C (2023) Safety profile of monoclonal antibodies targeting the calcitonin gene-related peptide system in pregnancy: updated analysis in VigiBase®. Cephalalgia 43(4):3331024231158083
62. Noseda R, Bedussi F, Gobbi C, Ceschi A, Zecca C (2024) Calcitonin gene-related peptide antagonists in pregnancy: a disproportionality analysis in VigiBase(®). J Headache Pain 25(1):10
63. Wong HT, Khalil M, Ahmed F (2020) OnabotulinumtoxinA for chronic migraine during pregnancy: a real world experience on 45 patients. J Headache Pain 21(1):129
64. Brin MF, Kirby RS, Slavotinek A, Adams AM, Parker L, Ukah A et al (2023) Pregnancy outcomes in patients exposed to OnabotulinumtoxinA treatment: a cumulative 29-year safety update. Neurology 101(2):e103–e13
65. Smirnoff L, Moskatel L, Shaw B, He Z, Peretz A (2025) A retrospective cohort study to evaluate the effectiveness and safety profile of occipital nerve blocks in the treatment of migraine during pregnancy. Headache 65(10):1727–1733
66. Wojnar-Horton RE, Hackett LP, Yapp P, Dusci LJ, Paech M, Ilett KF (1996) Distribution and excretion of sumatriptan in human milk. Br J Clin Pharmacol 41(3):217–221
67. Amundsen S, Nordeng H, Fuskevåg OM, Nordmo E, Sager G, Spigset O (2021) Transfer of triptans into human breast milk and estimation of infant drug exposure through breastfeeding. Basic Clin Pharmacol Toxicol 128(6):795–804
68. Baker TE, Croop R, Kamen L, Price P, Stock DA, Ivans A et al (2022) Human milk and plasma pharmacokinetics of single-dose rimegepant 75 mg in healthy lactating women. Breastfeed Med 17(3):277–282

69. Guerzoni S, Baraldi C, Brovia D, Cainazzo MM, Castro FL, Pani L (2023) Monoclonal anti-CGRP antibodies in post-menopausal women: a real-life study. Acta Neurol Belg 123(3):1039–1047
70. Argyriou AA, Dermitzakis EV, Xiromerisiou G, Rikos D, Rallis D, Soldatos P et al (2024) Menopause and its impact on the effectiveness of fremanezumab for migraine prophylaxis: post-hoc analysis of a prospective, real-world Greek registry. Expert Rev Neurother 24(11):1119–1126
71. Metsähonkala L, Sillanpää M, Tuominen J (1997) Outcome of early school-age migraine. Cephalalgia 17(6):662–665
72. Bille B (1997) A 40-year follow-up of school children with migraine. Cephalalgia 17(4):488–491; discussion 7
73. Zwart JA, Dyb G, Holmen TL, Stovner LJ, Sand T (2004) The prevalence of migraine and tension-type headaches among adolescents in Norway. The nord-trøndelag health study (head-HUNT-Youth), a large population-based epidemiological study. Cephalalgia 24(5):373–379
74. Milovanović M, Jarebinski M, Martinović Z (2007) Prevalence of primary headaches in children from Belgrade, Serbia. Eur J Paediatr Neurol 11(3):136–141
75. Slater S, Crawford MJ, Kabbouche MA, LeCates SL, Cherney S, Vaughan P et al (2009) Effects of gender and age on paediatric headache. Cephalalgia 29(9):969–973
76. Sillanpää M, Saarinen MM (2018) Long term outcome of childhood onset headache: a prospective community study. Cephalalgia 38(6):1159–1166
77. Stewart WF, Linet MS, Celentano DD, Van Natta M, Ziegler D (1991) Age- and sex-specific incidence rates of migraine with and without visual aura. Am J Epidemiol 134(10):1111–1120
78. Gupta S, McCarson KE, Welch KM, Berman NE (2011) Mechanisms of pain modulation by sex hormones in migraine. Headache 51(6):905–922
79. Gaßmann J, Barke A, van Gessel H, Kröner-Herwig B (2012) Sex-specific predictor analyses for the incidence of recurrent headaches in German schoolchildren. Psychosoc Med 9:Doc03
80. Vetvik KG, Benth J, MacGregor EA, Lundqvist C, Russell MB (2015) Menstrual versus non-menstrual attacks of migraine without aura in women with and without menstrual migraine. Cephalalgia 35(14):1261–1268
81. Vetvik KG, MacGregor EA (2021) Menstrual migraine: a distinct disorder needing greater recognition. Lancet Neurol 20(4):304–315
82. MacGregor EA (2004) Oestrogen and attacks of migraine with and without aura. Lancet Neurol 3(6):354–361
83. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A (2006) Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. Neurology 67(12):2154–2158
84. Pringsheim T, Gooren L (2004) Migraine prevalence in male to female transsexuals on hormone therapy. Neurology 63(3):593–594
85. Eikermann-Haerter K, Baum MJ, Ferrari MD, van den Maagdenberg AM, Moskowitz MA, Ayata C (2009) Androgenic suppression of spreading depression in familial hemiplegic migraine type 1 mutant mice. Ann Neurol 66(4):564–568
86. van Oosterhout, WPJ, Schoonman GG, van Zwet Ew, Dekkers OM, Terwindt GM, MaassenVandenbrink A et al (2018) Female sex hormones in men with migraine. Neurology 91(4):e374–e81
87. Dourson AJ, Darken RS, Baranski TJ, Gereau RW, Ross WT, Nahman-Averbuch H (2024) The role of androgens in migraine pathophysiology. Neurobiol Pain 16:100171
88. Bolay H, Ozge A, Saginc P, Orekici G, Uludüz D, Yalın O et al (2015) Gender influences headache characteristics with increasing age in migraine patients. Cephalalgia 35(9):792–800
89. Bugge NS, Vetvik KG, Alstadhaug KB, Braaten T (2025) Migraine through puberty and menopausal transition-data from the population-based Norwegian women and health study (NOWAC). J Headache Pain 26(1):145
90. Santoro N, Brown JR, Adel T, Skurnick JH (1996) Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab 81(4):1495–1501
91. Hall JE (2015) Endocrinology of the menopause. Endocrinol Metab Clin N Am 44(3):485–496
92. MacGregor EA (2020) Menstrual and perimenopausal migraine: a narrative review. Maturitas 142:24–30
93. Karlı N, Baykan B, Ertaş M, Zarifoğlu M, Siva A, Saip S et al (2012) Impact of sex hormonal changes on tension-type headache and migraine: a cross-sectional population-based survey in 2, 600 women. J Headache Pain 13(7):557–565
94. Pavlović JM, Stewart WF, Bruce CA, Gorman JA, Sun H, Buse DC et al (2015) Burden of migraine related to menses: results from the AMPP study. J Headache Pain 16:24
95. Martin VT, Pavlovic J, Fanning KM, Buse DC, Reed ML, Lipton RB (2016) Perimenopause and menopause are associated with high frequency headache in women with migraine: results of the American migraine prevalence and prevention study. Headache 56(2):292–305
96. Nappi RE, Sances G, Detaddei S, Ornati A, Chiovato L, Polatti F (2009) Hormonal management of migraine at menopause. Menopause Int 15(2):82–86
97. Sacco S, Merki-Feld GS, Ægidius KL, Bitzer J, Canonico M, Gantenbein AR et al (2018) Effect of exogenous estrogens and progestogens on the course of migraine during reproductive age: a consensus statement by the European Headache Federation (EHF) and the European Society of contraception and reproductive Health (ESCRH). J Headache Pain 19(1):76
98. Allais G, Castagnoli Gabellari I, De Lorenzo C, Mana O, Benedetto C (2011) Oral contraceptives in migraine therapy. Neurol Sci 32(Suppl, 1):S135–9
99. Løkkegaard E, Nielsen LH, Keiding N (2017) Risk of Stroke with various types of menopausal hormone therapies: a National cohort study. Stroke 48(8):2266–2269
100. Ornello R, Caponnetto V, Frattale I, Sacco S (2021) Patterns of migraine in postmenopausal women: a systematic review. Neuropsychiatr Dis Treat 17:859–871
101. Glaser R, Dimitrakakis C, Trimble N, Martin V (2012) Testosterone pellet implants and migraine headaches: a pilot study. Maturitas 71(4):385–388
102. Amundsen S, Nordeng H, Nezvalová-Henriksen K, Stovner LJ, Spigset O (2015) Pharmacological treatment of migraine during pregnancy and breastfeeding. Nat Rev Neurol 11(4):209–219
103. Headaches in pregnancy and postpartum: ACOG clinical practice guideline No. 3. Obstet Gynecol, 2022 139(5):944–972
104. Demirkaya S, Vural O, Dora B, Topçuoğlu MA (2001) Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. Headache 41(2):171–177
105. Spiteri JA, Camilleri G, Piccinni C, Sultana J (2023) Safety of drugs used for the treatment of migraine during pregnancy: a narrative review. Expert Rev Clin Pharmacol 16(3):207–217
106. MacGregor EA (2014) Migraine in pregnancy and lactation. Neurol Sci 35(Suppl, 1):61–64
107. Østensen M, Khamashta M, Lockshin M, Parke A, Brucato A, Carp H et al (2006) Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther 8(3):209
108. Worthington I, Pringsheim T, Gawel MJ, Gladstone J, Cooper P, Dilli E et al (2013) Canadian Headache Society guideline: acute drug therapy for migraine headache. Can J Neurol Sci 40(5 Suppl 3):S1–s80
109. Siminerio LL, Bodnar LM, Venkataramanan R, Caritis SN (2016) Ondansetron use in pregnancy. Obstet Gynecol 127(5):873–877
110. Russo A, Iannone LF, Orologio I, Rivi V, Boccalini A, Lo Castro F et al (2025) Safety of onabotulinumtoxin-A for chronic migraine during pregnancy and breastfeeding: a narrative review. Toxins (Basel) 17(4)
111. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB (2008) Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 48(8):1157–1168
112. Waliszewska-Prosół M, Grandi G, Ornello R, Raffaelli B, Straburzyński M, Tana C et al (2025) Menopause, perimenopause, and migraine: understanding the intersections and implications for treatment. Neurol Ther 14(3):665–680
113. Angerhöfer C, Hoehne CL, Ulrich M, Lange KS, Fitzek MP, Salim Y et al (2025) Sex-related disparities in migraine recognition and management: insights from a tertiary headache center cohort. J Headache Pain 26(1):225
114. https://www.ema.europa.eu/en/medicines/human/referrals/topiramate
115. https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances-0
116. Wells-Gatnik W, Martelletti P (2023) Antiseizure medications as migraine preventatives: a call for action for a teratogenic and neurodevelopmental risk removal. Expert Opin Drug Saf 22(9):777–781

Publisher's Note