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Review Article

Endocrine Triggers of Migraine: A Comprehensive Review

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ABSTRACT

Hormonal changes are increasingly understood as significant factors in the development and advancement of migraines, affecting both their frequency and clinical characteristics. The withdrawal of estrogen is a well-known trigger for migraines linked to menstruation, while consistently high levels of estrogen during pregnancy often provide a protective effect. Other hormones, such as progesterone, testosterone, prolactin, oxytocin, vasopressin and those produced by the thyroid, also contribute to migraine pathophysiology through their impact on pain regulation, blood vessel function and neuroinflammation. Recent studies indicate a two-way relationship between thyroid issues, specifically hypothyroidism, and migraines, along with the possible pain-relieving effects of testosterone and oxytocin. However, prolactin may increase the likelihood of migraines through pain-promoting mechanisms. This detailed review examines the role of significant hormones in the pathogenesis of migraines for both women and men, addressing their clinical implications for diagnosis, prevention and treatment. The discussion places particular focus on sex-related differences, hormonal therapies and the potential risks tied to hormonal contraception for women who experience migraines with aura. Additionally, the review emphasizes the necessity for personalized treatment strategies that consider hormonal influences and identifies future research pathways to address current knowledge gaps and enhance migraine management.


INTRODUCTION

Migraine is a prevalent neurological disorder that occurs in episodes and has a complex underlying mechanism. It presents as recurring attacks characterized by typically unilateral, often intense throbbing headaches, along with symptoms like

nausea, sensitivity to sound and sensitivity to light. Approximately one-third of those who suffer from migraines experience temporary neurological disturbances known as aura. (1) Migraine represents a significant global health issue, impacting over one billion individuals each year

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and ranking as the sixth most disabling condition globally, according to the World Health Organization. (2) A distinctive aspect of migraine is the notable difference in its prevalence and clinical characteristics between sexes. Women are more frequently affected, with migraines occurring two to three times greater in women than in men. This difference between genders is particularly noticeable following puberty, highlighting how hormonal elements contribute to the likelihood and severity of migraines. (2)(3) In women, variations in estrogen levels, particularly the rapid decline in estrogen during the menstrual cycle's late luteal phase, are strongly linked to the onset of migraines. In contrast, stable high levels of estrogen, such as those during pregnancy, are typically associated with a decrease in migraine occurrences. (1)(3) Hormones also impact migraines in men, although this aspect is not as widely investigated. Some studies suggest that lower levels of testosterone in men may correlate with a higher likelihood of experiencing migraines. Testosterone is believed to have a protective role by influencing pain pathways, decreasing cortical excitability, and affecting trigeminovascular activation. Despite men having a lower overall incidence of migraines, their episodes can be equally debilitating and often go undiagnosed because migraines are often viewed as a condition that mainly impacts women. (1)(3) The neurobiology of migraine entails the activation and increased sensitivity of the trigeminovascular system, cortical spreading depression, and disruptions in sensory processing. Sex hormones, including estrogens, progesterone, and androgens, play a crucial role in these processes. For instance, estrogens may increase neuronal excitability and facilitate cortical spreading depression, likely raising the risk of migraine attacks. (1)(2) Conversely, testosterone could mitigate these processes, which might account for the lower prevalence in men. (3)

Understanding the impact of hormonal changes in both genders is crucial for a thorough comprehension of migraine pathophysiology. While significant research has been directed towards estrogen's role in women with migraines, there is an increasing interest in investigating how testosterone and other hormones affect migraines in men. This review aims to assess the evidence regarding hormonal influences on migraines in both female and male populations, as well as to emphasize the consequences for diagnosis and treatment.

Pathophysiology

Migraine is a complicated and multi-dimensional brain disorder that can last for several days in total. Traditionally, migraine has been divided into four stages: the premonitory, aura, headache, and postdrome stages. While these stages can occur in a straightforward sequence, they often overlap significantly, making the simple linear progression both appealing and misleading. (2) Common triggers for migraines include red wine, menstrual cycles, hunger, lack of sleep, bright lights, hormonal changes, stress, strong scents, and periods of relaxation. Alternatively, certain factors can alleviate migraines, such as sleep, pregnancy, excitement, and the administration of triptans. Migraine susceptibility has a distinct genetic basis, with specific genetic mutations linked to unique forms of vascular headaches identified. For instance, the MELAS syndrome, which includes mitochondrial encephalomyopathy, lactic acidosis, and stroke-like incidents, is caused by a point mutation (A to G) in the mitochondrial gene coding for tRNA Leu(UUR) at a specific nucleotide position. (4)

Phases of migraine:

- **Premonitory Phase:** This stage is characterized by signs such as irritability,



tiredness, food cravings, and yawning. The underlying process involves the hypothalamus, brainstem, and diencephalon, influencing sensory processing and autonomic functions.

- **Aura Phase (If Present):** This stage presents symptoms such as visual disruptions and various temporary neurological signs, resulting from cortical spreading depression (CSD), a process characterized by a wave of depolarization in neurons and glial cells followed by a period of suppression.

- **Headache Phase:** The signs include a pounding headache, feelings of nausea, and sensitivity to brightness and noise. During this stage, the trigeminovascular system is activated, releasing neuropeptides (CGRP, substance P, neurokinin A), which results in pain and inflammation.

- **Postdrome Phase:** The symptoms include tiredness, difficulties with cognition, and alterations in mood. During this stage, persistent dysfunction in brainstem and cortical regions occurs after the headache has subsided.

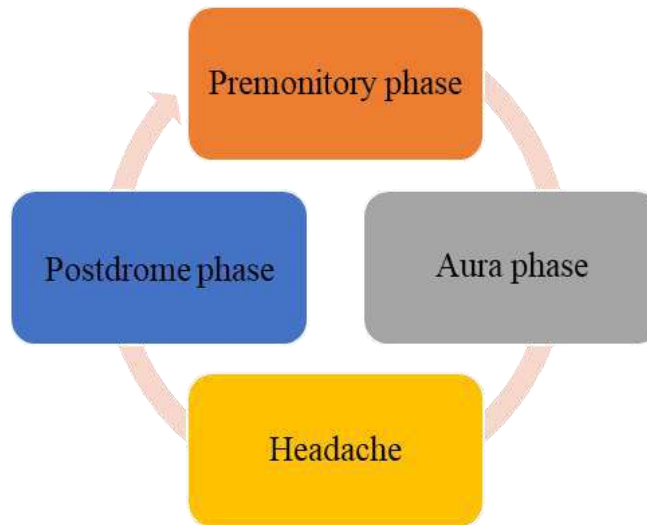


Fig. 1 Phases of Migraine

Early hypotheses suggested that migraines are linked to changes in serotonin levels. The effectiveness of triptans (agonists of the 5-HT_{1B/1D} receptors) reinforces the importance of serotonin in the mechanisms underlying migraines. The neuropeptide CGRP plays a significant role in the development of migraines, as it is released during episodes and promotes inflammation and vasodilation. Recent treatments, such as monoclonal antibodies against CGRP, focus on this specific pathway. (2)

Mechanisms involved in migraine:

1. **Cortical Spreading Depression (CSD):** A wave of depolarization occurs in both neurons and glial cells throughout the cortex. Cortical spreading depression (CSD) is seen as the electrophysiological basis of the migraine aura and a potential trigger for migraine attacks. During CSD, there is a considerable release of potassium ions, glutamate, nitric oxide, and other excitatory chemicals. These substances may stimulate trigeminal afferents that supply the meninges and pial blood vessels, starting nociceptive signaling. CSD is likewise linked with the release of neuropeptides, such as

CGRP, which facilitate neurogenic inflammation.

2. **Trigeminovascular System Activation:**

Engages trigeminal nerve fibers that supply the meninges and blood vessels. The initiation and sensitization of these fibers result in the relay of pain signals to the brainstem and subsequent areas of the cortex.

3. **Neurogenic Inflammation:** The secretion of CGRP and Substance P results in vasodilation, increased plasma leakage, and activation of mast cells. This ultimately leads to a prolonged sensitization of meningeal nociceptors, extending the duration of headaches.

4. **Role of CGRP:** A key neuropeptide involved in migraines facilitates vasodilation and inflammation. CGRP receptor antagonists serve as effective treatments. (1)

Historical perspective on migraine:

Migraine is a variable condition characterized by alternating periods of remission and relapse, with males more inclined to experience longer durations of remission compared to females. In a 40-year long-term study involving 73 Swedish children who were diagnosed with migraines between the ages of 7 and 15, it was found that 23% of the participants were free from migraines during puberty and early adulthood (34% of boys versus 15% of girls), and boys had a significantly higher chance of staying migraine-free. However, by the conclusion of the 40-year follow-up, when the participants were approximately 50 years old, 46% were no longer experiencing migraines, and there were no differences between sexes. (5) It remains uncertain if being female is also a contributing factor for the progression from episodic migraine to chronic migraine. An examination of the US AMPP study data indicated

that the likelihood of moving from episodic to chronic migraine was higher in women compared to men (odds ratio [OR] 2.9, 95% CI 1.2-6.9), even after adjusting for triptan use and headache frequency. (6)

Hormonal influence on migraine

1) Estrogen and Migraine:

In women who are not pregnant, the ovaries are the main producers of estrogens, with smaller amounts produced by adipose tissue, the liver, adrenal glands, and breast tissue. In men, estrogen is generated from its precursors, androstenedione and testosterone, through a process called aromatization. While estrogen levels in men are significantly lower than in young women, these levels remain relatively constant throughout a man's life and decrease more gradually with age. Consequently, men aged over 60 have around three times the amount of circulating estradiol compared to postmenopausal women who do not use supplemental estrogen. (7) Estrogen is primarily produced by the granulosa cells found in the ovaries of females of reproductive age. Nevertheless, various other tissues, including fat tissue, skin, bone, and the brain, can produce estrogen from androgen precursors through the enzyme aromatase. In both postmenopausal women and men, the importance of extraglandular (peripheral) estrogen production increases, with adipose tissue becoming a notable source due to its aromatase activity. In postmenopausal women, the heightened expression of aromatase in fat tissue can lead to physiological consequences, such as uterine bleeding or a greater risk of hormone-sensitive cancers. (8) Significant reductions in estrogen levels, as opposed to stable or increasing levels, are closely associated with the beginning of menstrually related migraines (MRM) and migraines with aura (MwA). Reducing the drop in estrogen levels can assist in preventing these types



of migraines. (7) A research project exploring variations in estrogen levels during the menstrual cycle in women who experience menstrual and menstrually associated migraines found that migraines were notably more likely to happen during periods of decreasing estrogen, especially in the late luteal to early follicular phase, which supports the estrogen "withdrawal" theory. Furthermore, migraines were significantly less frequent during phases of increasing estrogen. No correlation was observed between migraines and ovulation. We concur with the idea that a sustained high estrogen phase is a crucial precursor. (9)

Menstrual migraine:

Menstrually related migraines are characterized by episodes that occur during the first couple of days of menstruation for at least 3 consecutive cycles in at least 2 out of 3 menstrual cycles, and may also happen at other times during the cycle. In some women, their headaches do not correlate with their menstrual cycles. However, about 60% of women with migraines experience menstrually related migraines. Pure menstrual migraines are found in around 10%-14% of cases. (10) The drop in estrogen levels during the luteal phase is thought to trigger migraine attacks, and this decline may affect blood vessels, increasing their permeability to pro-inflammatory substances like prostaglandins. Prostaglandin levels are three times higher during the luteal phase, with an additional rise during menstruation, suggesting they may contribute to menstrually related migraines. (11) The estrogen withdrawal theory suggests that drops in plasma estrogen can initiate migraine attacks and neuroinflammation, potentially resulting in chronic sensitization. Several mechanisms could support this theory. One possibility is that estrogen reduces pain by interacting with estrogen receptor alpha (ER alpha) and estrogen receptor beta (ER beta), which

are primarily located in the nuclei of trigeminal ganglia. The activation of these nuclear receptors influences inflammatory genes, which ultimately decreases cell excitability. Additionally, this hypothesis might be further explained by reductions in estrogen that lead to elevated levels of calcitonin gene-related peptide (CGRP). (12) Despite the development of non-oral contraception methods, oral contraceptive pills (OCP) continue to be a preferred choice for many women; however, they can create complications in migraine sufferers who experience aura. (11) Hormone-free periods (which last 7 days in traditional 21/7 contraceptive regimens) can lead to migraines due to the decrease in estrogen levels. Research indicates that minimizing or eliminating the hormone-free period (for instance, through continuous or extended cycle approaches like the 24/4 regimens) may help decrease the occurrence, intensity, and length of migraines, particularly for those related to menstruation. However, combined oral contraceptives (COCs), especially those containing ethinylestradiol, carry an increased probability of stroke, particularly among women experiencing migraine with aura, as well as those who smoke or have additional cardiovascular risk factors. As a result, combined hormonal contraceptives (CHCs) are generally avoided in women experiencing migraines with aura unless stringent precautions are implemented. (13)

2) Progesterone and migraine:

While most research has concentrated on estrogen, the exact role of progesterone remains largely unexplored, though it is probable that progesterone also influences trigeminal nociception. Investigations into the hormonal impact on the receptive field sizes of trigeminal mechanoreceptors revealed no significant effects from progesterone treatment; however, other research indicated that allopregnanolone, a

metabolite of progesterone, can decrease activation in the trigeminal nucleus caudalis by engaging with GABAA receptors, implying a possible antinociceptive effect. More recently,

research has demonstrated that progesterone likely acts as a neurosteroid within peripheral sensory neurons and in the dorsal horn. (14) A progesterone

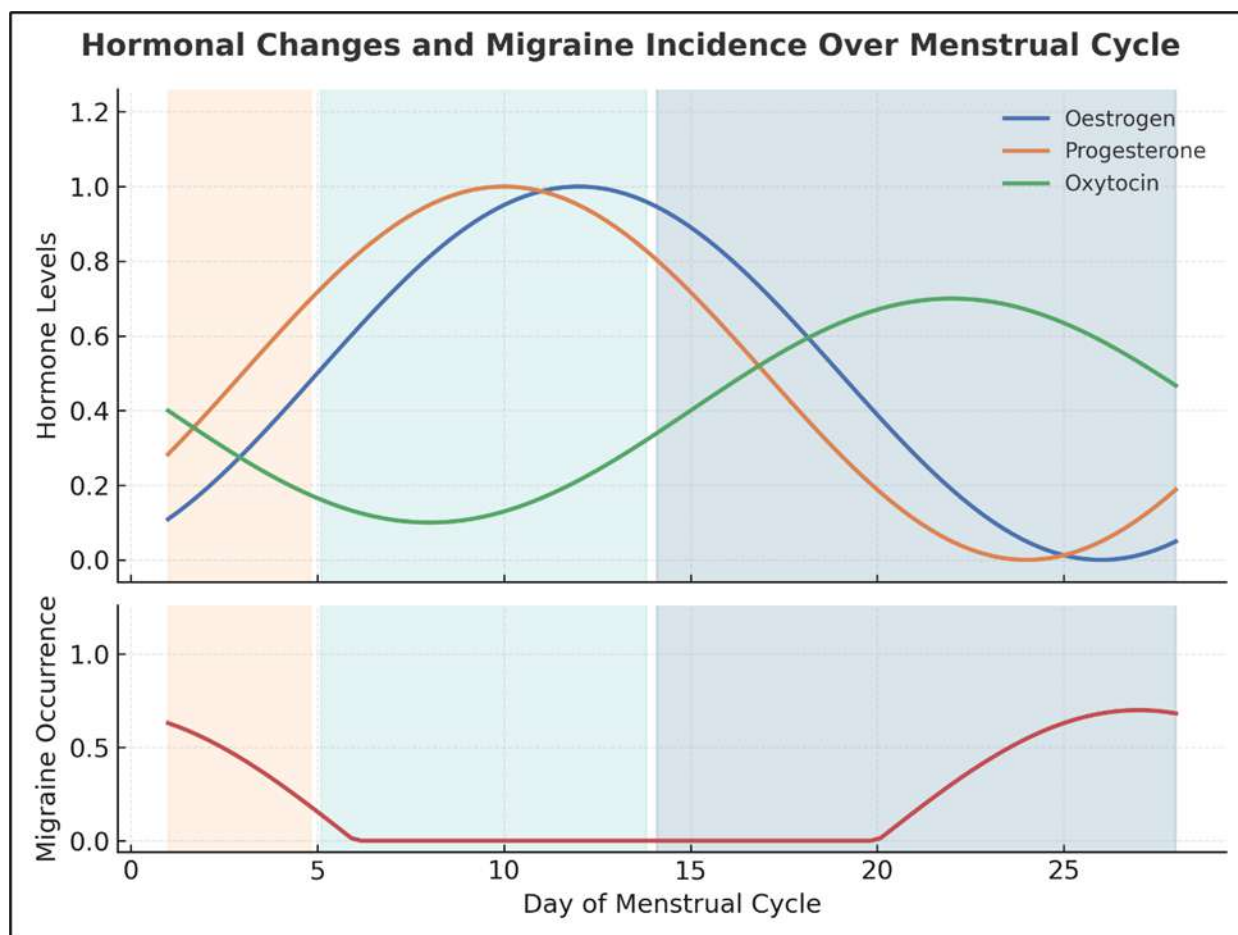


Fig. 2 Hormonal changes and migraine incidence over menstrual cycle

derivative is known to enhance GABA function by influencing GABA receptors, which subsequently reduces neuronal sensitivity. Moreover, both progesterone and allopregnanolone seem to mitigate nociception within the trigeminovascular network and help decrease neurogenic inflammation during migraines via interactions between neurons and glia. Additionally, in animal studies, progesterone and estradiol impact two central nervous system pathways that promote neuroprotection. At present, synthetic progesterone is utilized as a contraceptive and as a preventive treatment for migraines through the

administration of a continuous low dose of progestin. (12) A different experimental study demonstrated that progesterone enhances the secretion of calcitonin gene-related peptide (CGRP) and substance P (SP) in trigeminal ganglia, both of which contribute to neurogenic inflammation and the pain associated with migraines. Nevertheless, progesterone also reduces SP secretion from the peripheral ends of meningeal trigeminal nerves, indicating a possible site-specific anti-inflammatory effect. These opposing actions might help explain how hormonal changes impact the occurrence and

intensity of migraines in women. The results emphasize the necessity for further investigation to clarify progesterone's influence on migraine-associated neuropeptides and its potential therapeutic relevance. (15)

3) Testosterone and migraine:

Testosterone is crucial in regulating pain pathways and may provide a protective effect against migraines. Although commonly identified as a male hormone, testosterone also has significant physiological impacts in females. It seems that testosterone possesses antinociceptive effects, which lower pain sensitivity. Research indicates that animals with decreased testosterone levels, either due to castration or receptor inhibition, show heightened sensitivity to pain, a condition that can be reversed with testosterone treatment. (12), (14). In human studies, men suffering from migraines have been observed to have decreased testosterone levels than those without migraines, and these individuals often report symptoms associated with androgen deficiency, indicating that decreased testosterone might be a factor in migraine susceptibility. (12) Testosterone plays a important role in the regulation of pain pathways and may offer protective benefits against migraines. Although often regarded as a male hormone, testosterone also has significant physiological impacts on women. It seems that testosterone possesses antinociceptive properties, which help to lessen pain sensitivity. Research involving animals indicates that those with lower testosterone levels, whether due to surgical removal of the testes or receptor inhibition, show heightened sensitivity to pain, a condition that improves with testosterone therapy. In human studies, men with migraines tend to have lower testosterone levels compared to those without the condition, and they often report symptoms associated with androgen deficiency, implying that diminished testosterone could

increase the risk of migraines. (16) From a mechanistic perspective, testosterone may provide its positive effects by inhibiting cortical spreading depression (CSD), boosting serotonergic activity, stabilizing cerebral blood flow, and decreasing neuroinflammation. (12), (14). Although the results have been encouraging, testosterone is not yet part of the migraine treatment guidelines. It is necessary for additional large-scale, randomized controlled trials to determine its effectiveness, safety, and best application in both men and women suffering from migraines (12), (17).

4) Prolactin and migraine:

Lactotrophic cells situated in the anterior pituitary gland generate prolactin (PRL), a polypeptide hormone. It belongs to the prolactin/growth hormone/placental lactogen family and consists of 199 amino acids arranged in loops and alpha helices. (18) Prolactin is also synthesized by various other cell types, including mammary glands, ovaries, prostate gland, testes, endothelial cells, and adipose tissue. Initially identified in the 1930s for its role in regulating milk production and secretion, prolactin is now recognized as a multifunctional endocrine hormone with over 300 physiological roles. It is related with regulatory and modulatory functions across the endocrine, immune, and nervous systems and has been connected to the development of pain and headaches. Premonitory symptoms, such as food cravings and mood changes, have been connected to hypothalamic dysfunction, while disturbances in the hypothalamic–pituitary–gonadal (HPG) axis have been related to menstrual migraines. (19) Prolactin functions as a pronociceptive hormone, enhancing pain sensitivity in migraine sufferers. It amplifies the responsiveness of pain-related structures, particularly the trigeminovascular system, which is crucial to the mechanisms underlying migraine. The effects of prolactin are



more significant in females. Animal studies have demonstrated that administering prolactin can trigger migraine-like behaviors in female rodents, while this effect is not observed in males. Prolactin sensitizes TRP channels (such as TRPV1, TRPM8, TRPA1) found in sensory neurons, leading to increased neuronal excitability and altered pain perception. It also boosts the release of calcitonin gene-related peptide (CGRP), an important neuropeptide with relation to migraine, especially in females. Many migraine patients, particularly those experiencing chronic migraines, have been found to have elevated serum levels of prolactin. Treatments aimed at reducing prolactin levels, like dopamine D2 receptor agonists (for example, bromocriptine and cabergoline), can help lower how frequently migraine occurs, especially in individuals with prolactinomas. (20)

5) Oxytocin and migraine:

Oxytocin, a neuropeptide hormone, is influenced by estrogen and has properties that may alleviate migraines. Some research indicates that oxytocin could help in preventing migraine episodes, positioning it as a possible protective element for migraines linked to hormonal changes. Levels of both oxytocin and estrogen decrease during menstruation. The theory suggests that a decrease in oxytocin may diminish its pain-inhibiting (antinociceptive) effects, leading to an increased likelihood of experiencing migraines. (21) Neurons in the trigeminal ganglia have oxytocin receptors, many of which also contain CGRP, a substance that oxytocin can inhibit from being released; this is crucial because CGRP is pivotal in the development of migraines. Oxytocin may also suppress the activity of neurons in the trigeminal nucleus caudalis (TNC), which could lead to a reduction in pain signaling triggered by harmful stimuli such as facial shocks or nitroglycerin infusion, a model for migraines. In animal studies,

delivering oxytocin via the nasal route was shown to specifically target the trigeminal system. More than 80% of neurons in the trigeminal ganglia that express oxytocin receptors also co-express CGRP. The reduction of CGRP release by oxytocin may account for its potential to lower the frequency of migraines, similar to the action of anti-CGRP monoclonal antibodies. (22)

6) Other reproductive hormones:

• Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH):

Although the connection of sex hormones like estrogen and progesterone to migraine development is well recognized, the implications of gonadotropins such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are less understood. In a study conducted by Pavlović et al. (2016), researchers investigated the link between daily hormone levels and migraines in a large, diverse group of pre- and early perimenopausal women. The study particularly analyzed peak hormone concentrations and the rate of change in FSH and LH levels among women with migraine history compared to those without. The results indicated no notable differences in either the absolute hormone levels or daily variations of FSH and LH between the two groups. (23) These results differ from those presented by Li et al. (2018), who found that levels of FSH and LH had a positive association with the progression of headaches and scores related to migraine disability, especially in male patients with migraines and in women while in the luteal phase. (24) This difference implies that although abnormalities in gonadotropin levels might be detected in certain migraine populations, especially when examined in a cross-sectional manner, they may not consistently indicate a hormonal profile specific to migraines when

variations in hormone levels are monitored over time, as demonstrated by Pavlović et al.

7) Vasopressin and migraine:

Arginine vasopressin (AVP) is a neuropeptide hormone that exhibits an antidiuretic effect in low doses, while in higher doses, it leads to vasoconstriction. This neuropeptide is produced in the hypothalamus and is essential for regulating water balance, vascular tone, and pain perception. Numerous studies have explored its role in the pathogenesis of migraines and its possible therapeutic uses. AVP functions as an adaptive neurohormone during migraine episodes. Although AVP may not be a direct trigger for migraines, its levels rise in reaction to stress, nausea, and vomiting common symptoms that occur during attacks of migraine. Increased levels of AVP during such episodes might provide antinociceptive benefits by promoting fluid retention and stabilizing vascular tone. The research also presented evidence showing that administering AVP intranasally can alleviate headache symptoms in a dose-dependent fashion (100–400 ng), indicating its potential as a treatment option. (25) It also plays a role in regulating plasma osmolality and blood pressure, which are crucial elements affecting the onset and intensity of migraines. Variations in vasopressin secretion are connected to various stages of migraine episodes. Increased levels of AVP have been associated with migraines triggered by stress, whereas lower levels are observed during the recovery phase. Although results regarding serum AVP levels are inconsistent, its importance in maintaining homeostasis and managing nociceptive pathways is still notable. (26) Research has noted an increase in vasopressin receptors on platelets in individuals suffering from migraines, suggesting that the sensitivity of these receptors is heightened rather than there being

elevated levels of plasma AVP. This increased sensitivity could play a role in the vascular alterations and platelet clumping seen in the pathogenesis of migraines. This effect seems to be more significant in women, which may help to clarify the greater frequency of migraines among females compared to males. (27) The intranasal administration of AVP has been shown to enhance its levels in both cerebrospinal fluid (CSF) and plasma, which are linked to decreased headache intensity. This method of delivery avoids the blood-brain barrier by utilizing the olfactory route, facilitating direct effects on the central nervous system. The pain-relieving characteristics of AVP through central modulation emphasize its promise as a new therapeutic approach for managing migraines. (28) Although vasopressin has not undergone as much research as hormones such as estrogen or oxytocin regarding migraines, its influence on autonomic regulation and pain processing deserves additional exploration. Gaining a deeper understanding of how vasopressin interacts with other hormonal elements could offer fresh perspectives on the intricate neuroendocrine processes involved in migraines, potentially leading to more precise treatment approaches. (12)

8) Thyroid hormones and migraine:

Thyroid dysfunction, especially hypothyroidism, is notably linked to migraines. Observational research indicates a two-way connection, where experiencing migraines increases the probability of developing thyroid dysfunction, and hypothyroidism heightens both the occurrence and intensity of migraines and tension-type headaches. (29). Thyroid hormones (TSH, fT3, fT4) play important role in regulating neurovascular function, maintaining neurotransmitter levels, and processing pain. Potential effects of hypothyroidism include altered cerebral blood



flow, increased pain sensitivity, and disruption of serotonin and dopamine pathways, all of which may contribute to the mechanisms behind migraines. (30), (31) Research in genetics has demonstrated a common vulnerability between migraines and thyroid issues. Variants in the MTHFR, THADA, and ITPK1 genes have been related to both conditions, suggesting shared biological mechanisms. (29) Clinically, reduced TSH levels are linked to extended headache duration and less effective treatment responses, while elevated TSH levels correlate with improved outcomes in migraines. (31) Some migraine patients experience headache improvement with thyroid hormone replacement therapy, reinforcing the functional link between thyroid status and migraine. (30)

❖ **Clinical implications and Treatment considerations**

Hormonal changes, especially those related to estrogen and progesterone, significantly facilitate the advancement and symptoms of migraines. This effect is particularly evident in women, who suffer from migraines much more frequently than men, often due to the cyclical patterns of ovarian hormones. Migraines are known to be triggered by estrogen withdrawal. A decrease in estrogen levels right before menstruation can heighten cortical excitability, leading to cortical spreading depression, which is associated with the starting of migraine aura and headaches. Estrogen also affects blood vessel function and the modulation of serotonin, both of which are involved in the development of migraines. (32), (33) Progesterone positively influences the central nervous system by boosting GABAergic transmission and lowering the activity of monoamine oxidase. Consequently, this leads to elevated serotonin levels, which may help alleviate both migraine and depressive symptoms. (32) Menstrual migraines, which are

triggered by estrogen decline in the late luteal phase, tend to be more intense, persist longer, and are less likely to respond to immediate treatments compared to migraines not associated with menstrual cycles. Following menopause, the stabilization of hormone levels can result in an improvement in migraines, although the use of hormone replacement therapy (HRT) needs to be considered carefully. High doses of estrogen therapy might worsen migraine, especially in those with aura, while a continuous low-dose approach appears to yield more favorable results. Pregnancy, particularly during the second and third trimesters, is often linked with stable and elevated estrogen levels, frequently resulting in a decrease in both the frequency and intensity of migraines. Due to hormonal variations, tailored treatment strategies are essential. For menstrual migraines, using NSAIDs or triptans as prevention throughout the time before menstruation can be beneficial. Hormonal treatments like continuous or extended-cycle combined oral contraceptives (COCs) can help stabilize hormonal changes, but they come with risks, especially for women who experience migraines with aura, as there is higher chance of ischemic stroke, particularly when combined with smoking or other vascular risk factors. It is crucial to exercise caution when prescribing estrogen-containing contraceptives to women with migraines with aura because of the heightened stroke risk. Non-hormonal contraceptive methods or progestin-only options may be safer choices for these individuals. (33), (34)

Treatment Considerations:

Successful management of migraines necessitates a comprehensive and personalized strategy that takes into account the patient's medical history, accompanying conditions, genetic factors, and social influences such as sex and gender. Both



immediate and preventive treatments must be thoughtfully customized to alleviate the impact of the condition, curb medication overuse, and enhance the overall quality of life.

1) Acute Migraine Treatment:

Acute treatment aims for rapid, consistent relief of migraine attacks, ideally with little side effects. Strategies include:

- **Non-specific agents:** Such as NSAIDs (e.g., ibuprofen, aspirin, naproxen) are considered first-line for mild-to-moderate migraines. (35)
- **Triptans (serotonin receptor agonists):** These are first-line for moderate-to-severe migraines, particularly when NSAIDs fail. They should be used early in an attack for maximum efficacy. (35)
- **Combination therapies:** Such as sumatriptan with naproxen sodium, have demonstrated superior efficacy to monotherapy in acute treatment. (35)
- **Emerging therapies:** Such as gepants (e.g., ubrogepant) and ditans (e.g., lasmiditan), offer alternatives for patients with cardiovascular contraindications to triptans. (35)

2) Preventive Migraine Treatment:

Preventive treatment is advised for individuals who experience frequent or debilitating attacks. The objectives are to decrease the frequency, severity and length of attacks while enhancing the effectiveness of acute treatments.

- First-choice preventive medications consist of beta-blockers (such as propranolol and metoprolol), antiepileptics (including topiramate and valproate), and antidepressants (like amitriptyline). Nutraceuticals such as

magnesium, riboflavin, and coenzyme Q10 are also commonly utilized. (36)

- Botulinum toxin type A (BoNT-A) has received FDA approval in order to avoid chronic migraines. It decreases both peripheral and central sensitization and is effective in patients who suffer from medication overuse. (37)
- CGRP monoclonal antibodies represent a newer treatment option aimed at the calcitonin gene-related peptide pathways, providing preventive advantages for both episodic and chronic migraine. (35)

3) Pharmacogenetic Considerations:

Genetic differences, especially in drug-processing enzymes (such as CYP450 isoenzymes), play an important role in the effectiveness and tolerability of treatments for migraines. Pharmacogenetic analysis has the potential to facilitate tailored therapies, enhance effectiveness, and reduce side effects. People can be classified as poor, intermediate, extensive, or ultra-rapid metabolizers based on variations in their CYP genes, which influences how they respond to common medications like triptans and beta-blockers. Incorporating pharmacogenetic testing into everyday clinical practice could assist in choosing the right treatments and appropriate dosages. (36)

4) Sex and Gender-Specific Considerations:

Fluctuations in hormones, especially the decrease in estrogen levels, are a significant factor that triggers migraines in women. Managing menstrual migraines calls for personalized approaches, which may include short-term preventative measures using NSAIDs or triptans, along with cautious application of hormonal treatments.

Women tend to endure more intense migraine symptoms (like nausea and photophobia) and a greater degree of disability. When considering hormone replacement therapy (HRT) and combined hormonal contraceptives for women with migraines, particularly those experiencing aura, it is necessary to conduct a thorough evaluation due to the heightened risk of stroke. In transgender individuals, the effects of gender-affirming hormone therapies can alter migraine patterns, requiring careful observation and customized treatment strategies. (38)

5) Chronic Migraine and Medication Overuse:

Chronic migraine frequently occurs alongside medication overuse headache (MOH). Preventive therapies such as BoNT-A and CGRP monoclonal antibodies have demonstrated effectiveness in decreasing medication overuse and enhancing the frequency of headaches. Ideal candidates for BoNT-A are individuals suffering from chronic migraine (15 or more headache days per month) and medication overuse. Sustained treatment with BoNT-A may lead to improved effectiveness over a longer duration. (39)

❖ Future Research Directions

Despite recent progress, there are still several shortcomings in the research and management of migraines. Future efforts should focus on investigating non-CGRP therapeutic targets such as pituitary adenylate cyclase-activating polypeptide (PACAP), vasoactive intestinal peptide (VIP), amylin, and ion channels (TRP, ASICs) to fill the treatment voids for CGRP non-responders. (40), (41) More genetic and biomarker research is essential to facilitate personalized treatment strategies. Developments in neuromodulation techniques and behavioral methods (such as cognitive-behavioral therapy) offer promising non-pharmacological alternatives.

(41) Studies examining gender and sex variations, including investigations into the effects of hormones and gender-affirming therapies, is essential for enhancing personalized treatment approaches. Globally, the increasing prevalence of migraine, particularly in adolescents and males, underscores the necessity for specific public health initiatives and better accessibility to healthcare, especially in low- and middle-income countries. (42) Long-term real-world studies are vital to evaluate the efficacy and security of novel therapies. (40)

CONCLUSION

Migraine is a complicated neurological condition featuring a variety of underlying causes, with hormonal factors being particularly significant. Changes in sex hormones especially estrogen, progesterone, testosterone, prolactin, oxytocin, and thyroid hormones play an important role in influencing the likelihood, the occurrence and intensity of migraines. Research highlights that fluctuations in hormones, notably the drop in estrogen during the menstrual cycle, pregnancy, and menopause, are key triggers for migraines in women. Likewise, hormonal imbalances such as low testosterone levels in men, high prolactin levels, and thyroid disorders are increasingly recognized as vital contributors to migraine development in both sexes. Grasping the complex interactions between hormones and migraines carries important clinical implications. Hormonal therapies, which include options like hormonal contraceptives, hormone replacement therapy, and targeted treatments such as CGRP antagonists and vasopressin analogs, present promising avenues but necessitate careful patient evaluation due to potential risks, especially in cases of migraine with aura. Customized approaches that take into account hormonal levels, genetic factors, and sex-specific considerations are vital for enhancing

migraine management. Despite notable progress, there are still gaps in completely understanding how endocrine factors influence migraines. Future studies should focus on large-scale, long-term, and mechanistic research that investigates the connections between hormones and migraines, gender-affirming treatments, and new hormonal targets. A deeper insight into these relationships will facilitate more effective and tailored treatment options, leading to better outcomes for individuals suffering from migraines.

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