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Review

Migraine Throughout Women's Reproductive Life: Unravelling the Cardiovascular and Metabolic Implications

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Abstract

Background/Objectives: Migraine is a leading cause of disability in women and is intricately linked to hormonal fluctuations and systemic health. This review aims to unravel the complex relationship between migraine, cardiovascular disease, and metabolic syndrome throughout the female reproductive lifespan. **Methods**: A comprehensive narrative review was conducted using the PubMed database for studies published between January 1988 and December 2025. Keywords included "migraine", "cardiovascular risk", "metabolic syndrome", "pregnancy", and "hormonal therapy". Articles were selected to synthesize the latest pathophysiological evidence and clinical guidelines. **Results**: Migraine prevalence in women is two to threefold higher than in men, peaking during fertile age. Hormonal milestones, particularly estrogen withdrawal, trigger menstrual migraine. Metabolic syndrome is significantly more common in migraineurs than the general population. Obesity and insulin resistance have been associated with higher migraine attack frequency and severity. Experimental evidence suggests that hyperinsulinemia may sensitize TRPV1 receptors on trigeminal neurons and enhance CGRP release, potentially lowering the activation threshold for migraine attacks; however, direct confirmation of this pathway in humans remains limited. Furthermore, migraine with aura is linked to a doubled risk of ischemic stroke and increased risk of cardiovascular events. In pregnancy, migraine is an independent risk factor for stroke, myocardial infarction, and spontaneous coronary artery dissection. **Conclusions**: Migraine is a critical marker for cardiovascular and metabolic risk, necessitating routine screening and multidisciplinary management. Clinicians must prioritize cardiovascular counselling, metabolic evaluations, and careful monitoring in these patients, especially during pregnancy. Hormonal therapy choices should be individualized, preferring progestin-only contraceptives for those with aura and transdermal routes for hormone replacement therapy to minimize cardiometabolic impact.

Keywords: migraine; cardiovascular risk; metabolic syndrome; insulin resistance; pregnancy; hormonal contraception; hormone replacement therapy

Academic Editor: Osamu Hiraike

Received: 2 February 2026
Revised: 26 February 2026
Accepted: 28 February 2026
Published: 9 March 2026

1. Introduction

Migraine is a chronic neurological disorder characterized by episodic attacks of unilateral pulsating headaches lasting 4 to 72 h. It is usually associated with moderate to severe pain, it is aggravated by physical activity [1] and may be accompanied by other symptoms such as nausea, vomiting, photophobia and phonophobia [2]. The primary factors that commonly initiate migraine attacks often involve high stress levels, fatigue, various foods such as alcohol, drugs, smoking, weather changes and odors [3].

Two types of migraine can be distinguished using the International Classification of Headache Disorders: migraine without aura, presenting as a headache with specific attributes and concurrent symptoms mentioned above, and migraine with aura, characterized by transient focal neurological symptoms that typically precede or occasionally coincide with the onset of the headache [2].

The worldwide incidence of migraine has increased in the last 30 years. As shown by the Global Burden of Disease (GBD) 2019 Study, the projected global prevalence of migraine has risen from 721.9 million cases in 1990 to 1.1 billion in 2019. In the same year, the national age-standardized incidence rates for migraine varied between 692.6 and 1528.4 cases per 100,000 individuals, with Italy and Norway recording the highest rates [4].

The prevalence of migraine in childhood is comparable between sexes but post-puberty its incidence diverges, with a two to threefold increase in women compared to men. Approximately 17% of adult women satisfy the diagnostic criteria for migraine, compared to only 5.6% of men [5].

Throughout women's life, the clinical manifestations of migraine correlates with reproductive milestones showing a higher incidence around puberty with a peak during the fertile age and a decline post-menopause [6,7]. In addition, the occurrence of migraine attacks undergoes variations in pregnancy and 20–25% of females show an association between their headaches and the menstrual cycle [8]. Moreover, the use of combined hormonal contraception (CHC) or hormone replacement therapy (HRT) may uncover or influence migraine onset and manifestations [9].

Migraine represents an important individual and societal burden as it leads to marked reduction in health-related quality of life (HRQoL) [10]. This condition was even the third-highest ranked cause of disability for both males and females under the age of 50 in the GBD 2015 assessment [11].

Migraine, especially with aura, is associated with a higher risk of cardiovascular disease [12] and increasing evidence is showing that there may be a connection between this condition and metabolic alterations that constitute the Metabolic Syndrome (MetS) [13].

The aim of this narrative review is to analyse the correlation of migraine with cardiovascular and metabolic risk in women, emphasizing the significance of early diagnosis to improve clinical management in all the stages of women's life.

2. Materials and Methods

For our narrative review we conducted a comprehensive and clinically oriented search focusing on the association between migraine, cardiovascular risk and metabolic syndrome.

A structured, although non-systematic, search strategy was applied to the PubMed database covering studies published between January 1988 and December 2025.

Several combinations of the following keywords were used: "migraine", "women", "pregnancy", "cardiovascular risk", "metabolic syndrome", "hormonal contraception" and "hormonal replacement therapy". Abstracts were screened to identify relevant articles to include in our review. Paper selection was based on relevance to the topic, methodological quality, and impact in the field. Priority was given to meta-analyses, large cohort studies, randomized controlled trials, and international guidelines. Moreover, a manual search for

the references of all included articles was performed to ensure a comprehensive review of the literature.

Exclusion criteria were languages other than English, Italian or French and unavailable full-length texts.

Given the narrative design, this review does not follow PRISMA criteria, and potential selection bias cannot be excluded. Our aim was to integrate pathophysiological insights with clinical implications rather than to provide a quantitative meta-analysis.

3. Etiopathology and Pathophysiology

Migraine etiopathology is still not completely understood, but current research suggests a complex interaction between genetics, environment, metabolic and hormonal state (Figure 1) [14].

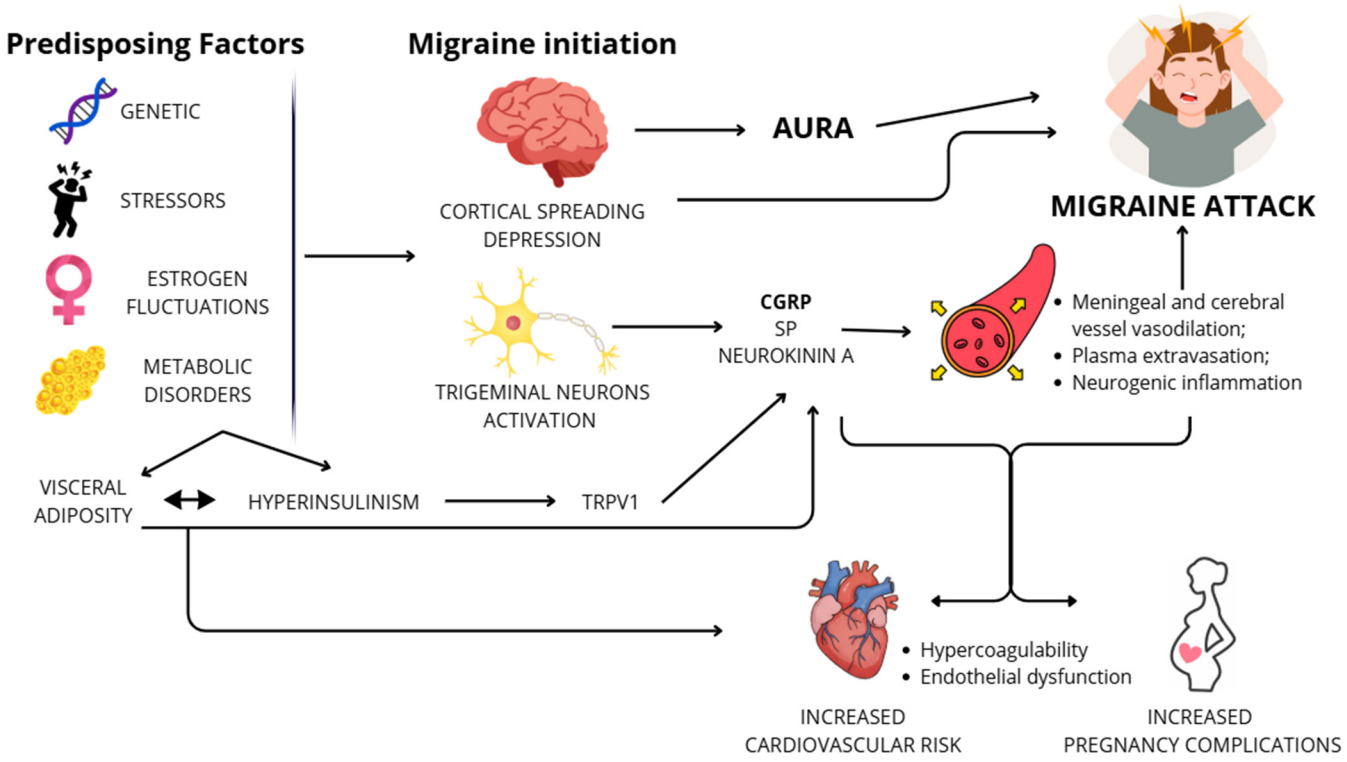

Figure 1. The etiopathology of migraine involves a complex interaction between genetic susceptibility, environmental stressors, and hormonal milestones. Estrogen fluctuations, particularly estrogen withdrawal, modulate neuronal inflammatory responses and favor the release of neuropeptides. Simultaneously, metabolic disorders play a critical role: visceral adiposity promotes a pro-inflammatory state that is often associated with hyperinsulinism, which may act as a potent sensitizer of Transient Receptor Potential Vanilloid 1 (TRPV1) receptors on trigeminal sensory neurons. Experimental models suggest that insulin may sensitize TRPV1 receptors, potentially lowering the activation threshold for Cortical Spreading Depression (CSD). Once triggered, trigeminal neurons seem to release vasoactive neuropeptides, including Calcitonin Gene-Related Peptide (CGRP), Substance P (SP), and Neurokinin A, which drive neurogenic inflammation characterized by meningeal and cerebral vessel vasodilation, plasma protein extravasation, and nociceptor sensitization. While these processes culminate in the clinical migraine attack and associated symptoms such as nausea and photophobia, they also carry significant systemic consequences. The chronic release of vasoactive factors and a pro-inflammatory mediators may contribute to endothelial dysfunction and hypercoagulability, significantly increasing the long-term risk for ischemic stroke, myocardial infarction, and atrial fibrillation, especially in women with aura. Furthermore, migraine serves as an independent risk factor for cardiovascular events during pregnancy and hypertensive disorders like preeclampsia, due to shared mechanisms of endothelial reactivity and obstetric vascular stress.

Despite the familial tendency of this neurological disorder, extensive genome-wide association studies have not revealed any genetic alterations linked to common migraine [15]. On the other hand, single gene mutations have been discovered for rare migraine syndromes suggesting that specific genetic variations may play a role in the manifestation of this condition [16].

The migraine attack is characterized by a typical temporal progression and four phases can be distinguished: (1) the premonitory phase, which precedes the onset of headache; (2) the aura phase, occurring immediately before or concurrent with the headache onset; (3) the headache phase itself; (4) the postdrome phase, manifesting after the resolution of the headache [17].

Certain manifestations of a migraine attack, such as sensory issues and neck pain, may persist throughout the entire attack. In contrast, other symptoms like the aura tend to have a fluctuating pattern [18].

Neuronal dysfunction may be responsible for the onset of migraine [19]; the headache and the presence of aura seem, in fact, associated with cortical spreading depression (CSD), as first described by Leão in 1944 [20].

CSD represents the spread of depolarization within neurons and glial cells throughout the cerebral cortex. This phenomenon is believed to be responsible for the aura experienced in migraine but could also activate the afferent nerves of the trigeminal system, influencing the permeability of the blood–brain barrier [21–23].

The trigeminovascular system represents the underlying anatomical and physiological foundation for migraine. It is formed by sensory pseudo-unipolar neurons that originate from the trigeminal ganglion and the upper cervical dorsal roots [24]. These neurons innervate various structures such as cerebral vessels, pial vessels or dura mater and ultimately converge at the trigeminal nucleus caudalis together with upper cervical nerve roots [19]. From this point, specific fibers that are responsible for the localization of pain ascend to the thalamus, to numerous subcortical sites and to the sensory cortex [25].

The activation of the trigeminal ganglion results in the liberation of vasoactive neuropeptides which include neurokinin A, substance P (SP), pituitary adenylate cyclase-activating peptide and calcitonin gene-related peptide (CGRP) [26].

Various studies showed elevated concentrations of these peptides in people suffering from migraine attacks [27]. CGRP, specifically, seems to be the principal mediator of migraines in the trigeminovascular system; it not only plays a role in transmitting pain signals from intracranial vessels to the central nervous system, but it also has vasodilatory effects and may have a role in neurogenic inflammation onset. Nonetheless, the exact pathways by which CGRP might trigger migraine episodes is still largely unknown [28].

Furthermore, migraine episodes frequently correlate to fluctuations in sex hormones plasma levels [29]. The discrepancy in prevalence between females and males, along with the alterations in migraine characteristics during the menstrual cycle and pregnancy [30], strongly link estrogen levels to the pathogenesis of this condition [31].

Estrogens have the ability to modulate the activity of several neurotransmitter systems involved in migraine pathophysiology and pain transmission; in particular, they enhance the serotonergic system, regulate the release of CGRP and SP with inhibitory effects and reduce neuronal inflammatory response interfering with the production of pro-inflammatory cytokines and circulating prostaglandins [8,9].

4. Migraine in Different Stages of Life

Migraine manifestation changes during women's stages of life and specific periods of susceptibility, mainly associated with fluctuations in estrogen levels, can be distinguished (Figure 2) [32].

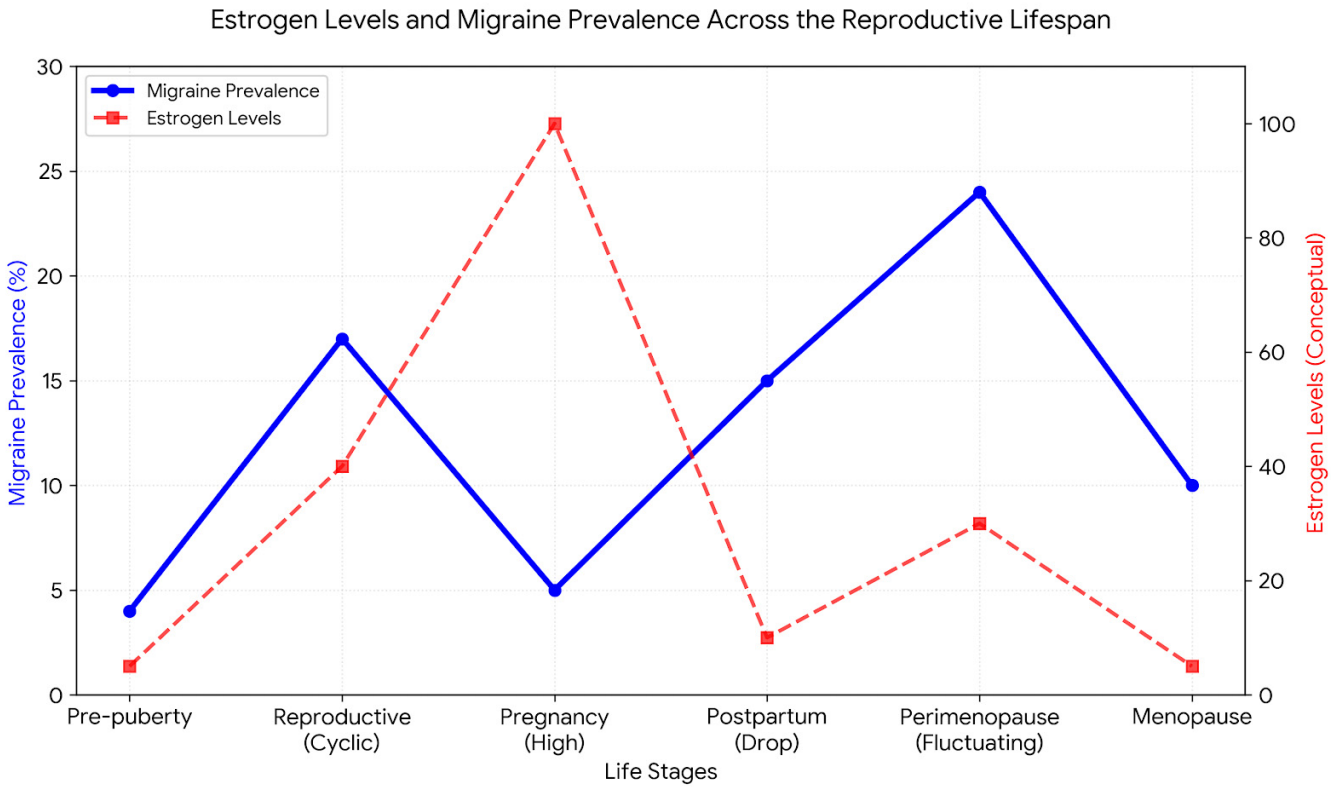

Figure 2. Conceptual schematic representation of the relationship between estrogen fluctuations and migraine prevalence across the female lifespan. Note the low prevalence during stable low-estrogen states (pre-puberty), the peak during cyclic fluctuations (reproductive age), the clinical improvement during both sustained high-estrogen states (pregnancy) and low-estrogen states (menopause), and finally the exacerbation during erratic hormonal fluctuations (perimenopause).

The prevalence of migraines in women increases between the ages of 10 and 12, just around the time of puberty. Prior to the age of 12, migraine prevalence ranges from 3.7% to 4.9%, with minimal difference between boys and girls [33].

In girls experiencing migraines with aura the highest incidence is observed at 12–13 years, meanwhile migraine without aura tends to reach its peak of incidence between 14 and 17 years [34].

It is possible that the irregular secretion of estrogen in postmenarcheal anovulatory cycles may contribute to the initiation of migraines with aura, while the establishment of the ovulatory menstrual cycle may contribute more to the onset of migraine without aura [35].

The International Classification of Headache Disorders 3 (ICHD-3) identified two types of menstrual migraine (MM): pure menstrual migraine (PMM), with or without aura, with an onset of attacks ranging from −2 to +3 days of menstruation occurring at least two of three consecutive menstrual cycles and no occurrence of headache at any other time of the cycle; and menstrual-related migraine (MRM) with or without aura occurring not only perimenstrually but also at other times of the menstrual cycle [2,8,9].

Menstruation is known to be a strong migraine trigger and by the end of their reproductive years up to 33% of women are estimated to have experienced at least one episode of MM. Moreover, MM attacks are more likely to be severe and resistant to abortive medications [36,37].

During the late follicular and early luteal phases, serum estradiol levels reach their highest point ranging between 100 and 400 pg/mL and then sharply decline to 25–50 pg/mL just before the onset of menstrual bleeding [38,39]. This reduction in estrogen levels is

thought to trigger MM as it might affect blood vessels, making them more susceptible to pro-inflammatory mediators like prostaglandins which are, on the other hand, increased during luteal phase and menstruation [6,35].

During pregnancy, especially in women with history of MM or migraine without aura, migraines frequently improve or even resolve entirely as estradiol levels steadily rise starting from the first trimester [40]. Findings from a prospective study, in fact, revealed a highly positive impact of pregnancy on migraine without aura with a significant reduction in frequency of migraine attacks (46.8%, first trimester; 83.0%, second; 87.2%, third) and complete remission reported by 78.7% of women at term. Additionally, none of the women from this study reported a worsening of symptoms and approximately 10% remained free of attacks throughout the entire pregnancy [41]. Moreover, the Akershus Birth Cohort Study in Norway revealed that pregnant women with self-reported MM had more intense headaches during early pregnancy and immediately postpartum in comparison to women without self-reported MM. Both groups demonstrated significant improvement during the second half of their pregnancies and directly after delivery [42].

Considering the above data, it is clear migraine without aura tends to be alleviated by the hyperestrogenic state typical of pregnancy and benefits from the absence of monthly hormonal fluctuations. On the other hand the high estrogenic milieu of pregnancy may trigger attacks of migraine with aura [43]. It has been shown that de novo migraines during pregnancy, which are uncommon (<3%), typically begin during the first trimester and manifest with aura [40,44,45]. There is also evidence that women with persisting headaches into the second trimester are less likely to experience improvement thereafter [46,47].

Migraines usually re-occur or worsen in the postpartum, due to the fast decline in estrogen levels. Breastfeeding seems to reduce migraine onset but despite the observed lower recurrence rates, Sances et al. showed that 55.3% of lactating migraineurs still experienced headaches within the initial month following delivery [41].

Typically, the perimenopausal phase begins around 45 years old and stable menopause is reached around the age of 55 [48]. This transition into menopause is characterized by hormonal instability and neuroendocrine pathways disarrangement [49]. In perimenopause the presence of fluctuating estrogen levels together with sleep disturbances or other climacteric manifestations may temporary exacerbate headaches [29]. The American Migraine Prevalence and Prevention Study investigated the impact of perimenopause on the frequency of migraine attacks in women aged 35–65 years and revealed a 1.4-fold increased risk of high-frequency headache (occurring >10 days per month) during the perimenopausal phase compared to the premenopausal stage [50].

The impact of menopause on migraines remains a topic of ongoing investigation. A prevailing trend suggests that women with a history of premenstrual syndrome and MM tend to experience improvement with age [51]. A retrospective study by Granella et al. found a reduced prevalence of migraines during menopause, with only 12% of 1300 women who had previously experienced migraines seeking consultation at a headache center during the postmenopausal years [52].

5. Migraine and Metabolic Syndrome

The MetS is a combination of various risk factors such as abdominal obesity, dyslipidaemia, glucose intolerance or hypertension and it identifies a population with elevated risk of cardiovascular morbidity and mortality [53]. In women, MetS prevalence (24–34%) is uniquely shaped by hormonal status [54–58].

Premenopausal estrogens offer a protective effect, favoring gynoid fat distribution and insulin sensitivity. However, the menopausal hypoestrogenism triggers a shift toward

android (visceral) adiposity, systemic inflammation, and a surge in hypertension prevalence which reach 72% in women aged 65–75 [59–61].

Moreover, other gender disparities are well known: while LDL cholesterol drives male risk, elevated triglycerides and Impaired Glucose Tolerance (IGT) are more potent predictors of female CVD mortality [62,63].

Understanding the correlation between migraine and metabolic disorders such as Insulin resistance (IR), obesity and MetS is still an ongoing challenge [13,64].

Guldiken et al. in 2009 examined 210 patients diagnosed with MetS according to NCEP/ATPIII criteria and assessed migraine prevalence using the International Classification of Headache Disorders-II (ICHD-II) criteria [13,65]. This study observed that migraine in patients with MetS was significantly more common than in general population, with a prevalence of 11.9% in men and 22.5% in women. Moreover, patients with migraine in this study showed higher mean BMI and waist circumference (WC), as well as an increased incidence of diabetes compared to the group with MetS without migraine [13]. The association between migraine and metabolic syndrome was then further confirmed in the Nord-Trøndelag Health Study (HUNT) [66].

It is also important to acknowledge that numerous evidence seem to establish correlations between the individual components of MetS and migraine.

Obesity and migraine often coexist in the general population and migraine prevalence tends to be higher in severely obese women [67]. Findings from Winter et al.'s prospective cohort study in the Women's Health Study did not find a significant association between migraine and overweight, obesity, or significant weight gain [68]. Nonetheless, a recent meta-analysis revealed a 27% increased risk of migraine in individuals with obesity compared to those with normal weight and in this same study underweight individuals had only a 13% increase in migraine risk [69]. Furthermore, obesity might contribute to migraine chronification and is associated with higher attack frequency; it has in fact been found that there seems to be a dose-dependent relationship between BMI and headache days [70,71].

WC is a marker of abdominal fat accumulation and indirectly correlates with IR and elevation in proinflammatory cytokine levels. Abdominal obesity in women is defined by the presence of a WC $\geq$ 88 cm. Peterlin et al. in 2010 demonstrated that in women under 55 years old, migraine prevalence was associated with abdominal obesity independently from BMI values [72]. However, in older women (>55 years old), migraine prevalence decreased if abdominal obesity was present [72]. Therefore, differences in visceral and subcutaneous adipose tissue may help explaining sex differences in migraine prevalence [72].

The higher prevalence of migraine associated with obesity and abdominal fat accumulation may have an inflammatory origin. Several studies have linked obesity to increased levels of inflammatory cytokines such as interleukin-6 (IL6) and tumor necrosis factor-α (TNF α), that may contribute to migraine pathogenesis [73,74]. Additionally, adipocytes release adipocytokines and particularly adiponectin, which has a pro-inflammatory effect and seems to be responsible for the increased activation of the nitric oxide pathway in the brain potentially triggering headache [75]. On the other hand, low levels of orexin in obese individuals may also be responsible for an increased susceptibility to neurogenic inflammation favoring migraine attacks [76,77].

Even if the causal relationship between migraine and obesity remains unclear, data from recent meta-analyses suggest that weight loss may improve migraine characteristics in patients with obesity, regardless of the intervention type (surgical vs. non-surgical) or the amount of weight lost [78].

Rainero et al.'s clinic-based study found notable changes in IR among young, non-obese, non-diabetic, normotensive migraine patients when compared to healthy controls [79].

Experimental evidence suggests that insulin might act as a potent sensitizer of the Transient Receptor Potential Vanilloid 1 (TRPV1) receptors on trigeminal sensory neurons. Prolonged hyperinsulinism may enhance nociceptive signaling via these channels, resulting in excessive CGRP release. This can cause neuroinflammation and likely reduces the migraine activation threshold, promoting CSD [80]. However, no association was found between migraine and type 2 diabetes, and type 1 diabetes even appeared to be protective [81,82]. Furthermore, findings from the E3N cohort study indicate a lower risk of developing type 2 diabetes among women with active migraine and a decrease in active migraine prevalence observed prior to diabetes diagnosis [83]. The apparent paradoxical association between increased IR in migraineurs and lower incidence of overt type 2 diabetes reported in large cohorts deserves careful interpretation [83]. Several hypotheses have been proposed. Chronic hyperglycemia and diabetes-related alterations in vascular reactivity and peripheral nerve function may theoretically increase the threshold for CSD, thereby reducing migraine susceptibility. Furthermore, behavioral and lifestyle modifications following a diabetes diagnosis could partially contribute to migraine improvement [81,84]. However, the association between migraine and diabetes remains incompletely understood and further longitudinal studies are needed to clarify temporal relationships.

Hypertension is a well-known risk factor for cerebrovascular disease [85]. A 2010 demographic study by Buse et al. showed a significant correlation between migraine, with or without aura, and high blood pressure [86]. Moreover, uncontrolled hypertension is believed to contribute to migraine chronification [87].

Dyslipidemia, characterized by elevated levels of triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C), seems to have an important impact on migraine onset. Various studies have shown that hypertriglyceridemia and low HDL-C levels are more prevalent in individuals with migraine, suggesting a potential association between impaired lipid profile and migraine pathophysiology [88,89].

Overall, the evidence suggests that each component of MetS independently contributes to migraine susceptibility and severity but more studies are needed to better understand the complex interplay between migraine and metabolism [90].

6. Migraine and Cardiovascular Disease

Numerous meta-analyses have linked migraine, particularly with aura, to a higher risk of CVD [12,91–93]. It has been demonstrated that women who suffer from migraine with aura are more likely to die from cardiovascular causes than those who do not have aura; therefore, the 2021 European Society of Cardiology (ESC) guidelines on cardiovascular disease prevention, considered migraine with aura in CVD risk assessment [94,95]. Moreover, migraine has been included in the algorithm of the QRISK3 score, a tool used to determine a person's 10-year risk of CVD if they are between the ages of 25 and 84 [96].

The Genetic Epidemiology of Migraine (GEM) study, a population-based study conducted in the Netherlands, provided data confirming that individuals with migraine show a higher prevalence of cardiovascular risk factors such as hypertension, hypercholesterolemia, smoking, and early familial myocardial infarction (MI) [97].

In addition, several studies have found a strong correlation between ischemic stroke and migraine [91]. A Swedish study involving 44,769 twins without migraine, and 8635 twins with migraine, of which 3553 with aura, observed an increased risk of stroke in twins with migraine with aura, but not in migraine overall [98]. According to recent meta-analyses, those with migraine aura have a doubled relative risk of ischemic stroke

compared to people without migraine [99,100]. However, there is still uncertainty about the risk of ischemic stroke for people with migraines without aura.

There is probably more than one molecular mechanism linking migraine and ischemic vascular events. Migraine is often associated with elevated levels of prothrombotic and vasoactive factors such as prothrombin, factor V Leiden, von Willebrand factor and endothelin. Furthermore, the release of vasoactive neuropeptides during migraine episodes may trigger inflammatory reactions [101–105]. Migraineurs with aura are also at increased risk of having patent foramen ovale (PFO), which can cause paradoxical embolism and cryptogenic stroke [106].

It has also been reported that migraine sufferers have an increased risk of haemorrhagic stroke, which may be related to the higher prevalence of hypertension in this population [107]. Despite robust evidence linking migraine, particularly with aura, to stroke, there is currently insufficient data to suggest treating migraine as a prophylactic measure against stroke [108].

Migraineurs tend to suffer more from angina pectoris and have an elevated risk of MI compared with people without migraine. While migraine without aura seems to be only marginally associated with an elevated risk of angina, this correlation is stronger among migraineurs who experience aura [92].

The Atherosclerosis Risk in Communities Study, a large cohort study with over 12,000 participants, discovered significant associations between angina and migraine, with a more significant correlation if migraine with aura were considered [109,110]. The relationship between migraine and angina pectoris resulting from coronary epicardial vasospasm was first documented thirty years ago. These studies showed a temporal correlation between the onset of the migraine attack and chest pain [111,112]. Several pathophysiological routes have been proposed for this connection. One of the theories is that migraineurs may have a higher prevalence of non-obstructive coronary artery disease due to systemic endothelial dysfunction [113], and another hypothesis consists of the presence of a dysfunction of the coronary microcirculation [114].

Recent investigations have observed a possible relationship between migraine with aura and atrial fibrillation (AF) [115,116]; encouraging outcomes in managing migraine symptoms have even been reported after catheter ablation of AF [117].

The importance of CGRP antagonists as a therapeutic target for migraine has emerged in recent years [118]. Nonetheless, CGRP receptors are located not only in the peripheral and central nervous system, but also in the cardiovascular system [119]. CGRP is a strong vasodilator and regulates vascular resistance and regional organ blood flow. Therefore, concerns have arisen regarding potential increased thrombotic complications with CGRP receptor blockage especially in patients with high cardiovascular risk [120,121]. However, current clinical data have not demonstrated a significant increase in severe adverse cardiovascular events in randomized trials or real-world registries [122].

In conclusion, a multitude of studies have shown the possible connection between migraine and CVD, for this reason it is important for physicians to ask about a patient's history of migraine when assessing cardiovascular risk.

7. Migraine and Pregnancy Related Cardiometabolic Implications

The impact of migraine on pregnancy has been greatly investigated. As previously discussed, fluctuations in female hormones modulate frequency and severity of migraines attacks and pregnant women tend to experience improvement in symptoms, particularly if they suffer from MM or migraine without aura [40].

Mohamet et al. published a systematic review and meta-analysis in 2025 that included more than 94 million pregnancies. They found that migraines and pregnancy-related

headaches are independent risk factors for a wide range of cerebrovascular and cardiovascular events during pregnancy and postpartum. Specifically, migraine was linked to higher chances of strokes, transient ischemic attacks, subarachnoid haemorrhage, myocardial infarction, peripartum cardiomyopathy, and spontaneous coronary artery dissection [123].

Beyond acute vascular events, migraine has also been linked to hypertensive disorders of pregnancy such as preeclampsia (PE) or gestational hypertension (GH) [124]. These conditions typically manifest after the 20th week of gestation and increase the risk of poor pregnancy outcomes. PE, in particular, affects 3–7% of pregnancies and contributes significantly to fetal and maternal morbidity and mortality worldwide [125,126]. The correlation between migraine and PE may be attributed to shared causal mechanisms such as altered endothelial reactivity and abnormal release of systemic inflammatory mediators [40].

Women who experience hypertensive disorders during pregnancy notoriously tend to have higher prevalence of hypertension, stroke and coronary heart disease even later in life [127].

Therefore, it can be assumed that migraine, GH, and PE may share common characteristics that increase the risk of developing ischemic disorders [120]. In fact, the latest guidelines from the European Society of Cardiology (ESC) recommend that women who have suffered from hypertensive disorders of pregnancy undergo long-term cardiovascular risk assessment and metabolic surveillance [123].

Both migraine and pregnancy are associated with hypercoagulability. Pregnancy is physiologically associated with a significant increase in plasma levels of procoagulant factors and a decrease in anticoagulant factors due to elevated estrogen levels [128]. Moreover, high levels of progesterone exert a compensatory vasodilatory effect, leading to venous dilation and blood stasis [129]. All these elements increase the risk of thrombotic events. For this reason, pregnant women with migraine, especially if the headache persists into the first trimester, are at higher risk of cardiovascular events and need careful monitoring [12,40].

A recent umbrella review conducted by Phillips et al. and published in 2024 showed that pregnant women with migraine had higher odds of preterm birth and peripartum mental illness. In this analysis, exposure to triptans during pregnancy was also associated with increased odds of miscarriage if compared with the healthy general population [130]. Finally, a small yet significant correlation between migraine and low birth weight was reported, consistent with previous findings by Aukes et al. [121,126]. The increased risk of hypertensive disorders in women with migraine, together with the need for medications like triptans during pregnancy, may contribute to a higher probability of delivering low birth weight infants [121,122].

Few studies have explored the relationship between migraine and gestational diabetes mellitus (GDM), but as for now, no conclusive evidence has been found [131,132]. Further research is needed to investigate the link between migraine and other pregnancy-related conditions, such as small for gestational age or placental abruption [130].

8. Influences of Hormonal Therapies on Migraine and Cardiometabolic Risk

Fluctuations in hormone levels, whether occurring naturally during menstrual cycles or induced by exogenous sex steroids like CHCs or HRT, influence the clinical presentation of migraine attacks [133–135].

CHCs play an important role in women's health, providing not only effective contraception but also managing other conditions such as heavy menstrual bleeding, pelvic pain, impaired androgen plasma levels or mood disorders [136,137]. This versatility in

addressing various health problems, together with the high prevalence of migraine in women, increases the likelihood of needing CHC use in individuals with migraine [138].

The primary concern regarding CHCs use in migraineurs is due to the increased risk of vascular disease. Stroke risk is already doubled in women with migraine with aura and can rise to sixfold with CHC use [139]. As a result, both the European Headache Federation and the European Society of Contraception and Reproductive Health recommend avoiding CHCs in patients with migraine with aura unless absolutely necessary [139]. Furthermore, medical eligibility criteria for contraceptive use suggest caution when prescribing CHCs also if migraine without aura is present [140–142].

On the other hand, progestin-only contraceptives (POCs), which have undergone extensive study in women with migraine, do not seem to increase risk for deep venous thrombosis, myocardial infarction, or thrombotic stroke when compared to CHCs, and this makes them the preferred therapeutic option in migraineurs [143]. Additionally, recent studies have shown that POCs may effectively prevent migraines with aura attacks. This improvement may be due to their ability to reduce plasma estradiol levels and to exert direct progestogenic effects on the brain, ultimately reducing CSD activation [144–146]. However, POCs' use is often associated with an irregular bleeding pattern that frequently leads to therapy discontinuation [147].

A separate discussion should be made for MM management, which is commonly associated with estrogen withdrawal during the menstrual cycle. Therefore, interventions that modulate estrogen fluctuations such as CHCs may prevent MM attacks [148]. This approach is based on the use of combined oral contraceptives (COCs) or alternative routes of administration, with continuous or flexible regimens in order to shorten the hormone-free interval and consequently reduce menstrual bleeding, making migraines more predictable, less frequent and less intense [9,149].

When selecting treatments for MM, it is important to choose formulations with very low doses of estrogen to minimize the vascular risk, especially if migraine attacks are associated with aura [150]. Modern CHCs containing less than 35 μg ethinylestradiol (EE) seem to be associated with a lower risk of ischemic stroke if compared to high-dose formulations [151–153]. Additionally, newer CHCs containing natural estrogens such as 17β-estradiol (E2), estradiol valerate (E2V), and estetrol (E4) may offer additional advantages, as they appear to be associated with fewer cardiovascular complications and metabolic alterations than EE [150,154,155].

Despite the potential benefits of CHC use in managing MM, it is important to recognize that there are currently no reliable tools to predict how migraines will respond to these interventions and while many patients may experience improvement in symptoms, others may find that their migraines worsen. For this reason, careful monitoring and an individualized approach are essential [156].

Beyond CHC administration, several studies have explored the efficacy of transdermal E2 patches during the perimenstrual period to prevent estrogen withdrawal and MM; however, none have demonstrated efficacy [157,158].

When counselling patients with migraines about the use of CHCs, it is of paramount importance to conduct a thorough assessment of their headache characteristics, evaluating the presence of aura or other cardiovascular risk factors in order to weigh the risks and benefits of these contraceptives against other options such as POCs or copper-releasing intrauterine devices [139,153].

We have already discussed the fact that migraineurs often notice a worsening of their headache during the menopausal transition, probably because of the erratic fluctuations in estrogen plasma levels. In such cases, CHCs or HRT may offer relief by not only regulating

menstrual cycles but also preventing estrogen withdrawal migraines along with other menopausal symptoms [159,160].

The impact of HRT on cardiovascular risk in women varies with endothelial health and timing of use. Typically, within 6 years of menopause or before age 60, it can have favorable long-term effects on cardiovascular markers and may reduce the risk of atherosclerotic disease [161,162].

Data from the Oxford Vascular Study (OXVASC) showed an increased risk of cryptogenic events and ischemic strokes among the users of HRT with migraine, but this association did not reach statistical significance. Moreover, this study lacked specific data on the type, dosage, duration, and route of administration of HRT [163,164]. According to an observational study by Nappi et al. HRT route of administration can greatly influence the course of migraines, and in particular, oral administration of HRT was found to exacerbate the frequency and intensity of migraine attacks, whereas transdermal therapy only had a minimal impact [165]. Therefore, transdermal E2, associated with progesterone with continuous combining regimens if the uterus is present, appears to be the best option to manage menopausal symptoms in women with migraine, especially in those experiencing aura [165,166]. Nevertheless, HRT, even if transdermal, should be discontinued immediately if there is a worsening in frequency or severity of migraine attacks or a new onset of aura [159].

The prevalence of MetS notably rises in menopause [167,168]. HRT has been shown to reduce perimenopausal changes in body composition and weight gain [169]. Moreover, its positive contributions extend into the postmenopausal stages, as it increases lean body mass and HDL cholesterol while reducing abdominal obesity and IR. All these effects are significantly protective with respect to cardiovascular risk [167]. However, it is important to note that oral HRT may increase triglycerides and decrease anticoagulant factors, such as protein S, although transdermal agents do not have these effects. As migraine tend to be associated with MetS and metabolic alterations, there is even more reason to prefer transdermal hormonal therapies in this population [13,66,90,168].

9. Conclusions and Recommendations

Migraine is a disease often underestimated and undiagnosed, despite its high prevalence and significant impact on quality of life. Many physicians only consider it noteworthy when aura is present, since there is a stronger correlation with CVD and stroke. However, this literature review shows that there is evidence linking migraine, even without aura, to cardiovascular risk and metabolic alterations.

Therefore, screening patients for migraines should be routine practice for all physicians. The International Headache Society has published classification and diagnostic criteria for migraine, but these may not always be practical for clinicians outside of neurology [2]. A more efficient option in a clinical setting may be the use of self-administered questionnaires, such as the three-item ID Migraine, which assesses women with headaches for symptoms typically associated with migraine, such as photophobia, impairment of daily function, and nausea [170].

The ID Migraine questionnaire is only a screening tool and yields a high rate of false positives; therefore, a complete evaluation is required to confirm migraine when a positive result is obtained [170].

Diagnosing aura can be even more challenging, but its identification is crucial as it is an important marker of increased stroke risk. Manifestations of the aura may include symptoms that are also associated with other serious neurological conditions, such as visual disturbances, sensory and speech alterations [171,172]. When assessing aura, clinicians should inquire about the duration and timing of symptoms associated with headaches.

Typically, aura precedes headache onset, lasts up to 1 h, and resolves before the headache begins [173].

Once a migraine diagnosis has been established, it becomes an essential element to consider when managing our patients' health. Individuals with migraines should receive counselling regarding their cardiovascular health and be encouraged to minimize other risk factors such as smoking or physical inactivity. Moreover, regular metabolic evaluations, including blood tests and clinical assessments for components of MetS should be conducted for early detection and treatment.

Women with migraine also need careful monitoring during pregnancy as they may be exposed to additional clinical risks, including onset of PE, stroke, thromboembolic events, as well as fetal growth alterations. These patients often require medications to manage their headaches, which may affect the fetus and should therefore be modified before seeking pregnancy. Furthermore, preliminary observational data have suggested a potential protective role of low-dose aspirin in selected high-risk pregnant women with migraine. However, evidence remains limited, and for the time being aspirin prophylaxis should follow established obstetric indications rather than migraine diagnosis alone [174].

Finally, the presence of migraine must also be considered when hormonal therapies are required (Table 1). For contraception, POCs are preferable if aura is present, as they have minimal impact on cardiovascular risk in migraineurs. However, when estrogen therapy is needed for other medical conditions, CHC administration should be attentively evaluated. In this case, it is essential to prioritize natural estrogens like E2, E2V or E4 over EE as they have lower cardiometabolic impact. Moreover, shortening the hormone-free interval could reduce fluctuations in hormone levels and improve MM control. Migraineur patients on CHCs, especially those with aura, should be closely monitored and treatment should be discontinued if significant worsening of headaches occurs.

Table 1. Management of hormonal therapies in women with migraine.

Reproductive Stage/ Clinical Need	Preferred Hormonal Approach	Rationale
Contraception (Migraine with Aura)	Progestin-Only Contraceptives (POCs)	Preferred due to reduced impact on cerebrovascular risk and potential to reduce CSD activation.
Contraception (Migraine without Aura)	POCs or CHCs (preferably with natural estrogens or low-dose EE)	POCs remain safest; if CHCs are used, natural estrogens (E2, E2V, E4) should be preferred over ethinylestradiol (EE) for lower cardiometabolic impact.
Menstrual Migraine (MM)	Extended/Continuous CHC regimens or shortened hormone-free Interval.	Aims to stabilize the estrogenic milieu and prevent the acute estrogen withdrawal that triggers migraine attacks.
Perimenopausal Transition	HRT or CHCs to stabilize fluctuations	Maintains a stable estrogenic milieu to address erratic fluctuations and associated climacteric symptoms.
Post-Menopause (HRT)	Transdermal 17β-estradiol (E2) at the lowest effective dose associated with progestins if uterus present.	Transdermal administration has a more favorable cardiovascular profile and lower impact on migraine frequency compared to oral HRT.

Maintaining a stable estrogenic milieu can be beneficial for migraine management during perimenopause, and it is important in addressing menopausal symptoms. While migraine with aura may contraindicate the use of contraceptives containing synthetic

estrogens, it does not preclude HRT. For these patients, the lowest effective estrogen dosage to treat menopausal symptoms with the transdermal route of administration should be preferred as it has more favorable effects on cardiovascular and metabolic parameters.

Author Contributions: Conceptualization, C.B. and R.E.N.; methodology, C.B. and R.E.N.; writing—original draft preparation, C.B.; writing—review and editing, V.V., A.D.G., P.C. and R.E.N.; visualization, C.B. and V.V.; supervision, A.D.G., P.C. and R.E.N.; project administration, R.E.N. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study.

Acknowledgments: The authors used OpenAI's large language model (ChatGPT 5.1) and Grammarly to improve the manuscript's fluency and readability. No content was generated by the model. All outputs were critically reviewed, edited, and approved by the authors.

Conflicts of Interest: The authors declare that there are no conflicts of interest with any financial organisation regarding the material discussed in the manuscript.

Abbreviations

The following abbreviations are used in this manuscript:

AF	Atrial fibrillation
BMI	Body mass index
CGRP	Calcitonin gene-related peptide
CHC	Combined hormonal contraception
COC	Combined oral contraceptive
CSD	Cortical spreading depression
CVD	Cardiovascular disease
E2	17β-estradiol
E2V	Estradiol valerate
E4	Estetrol
EE	Ethinylestradiol
GBD	Global Burden of Disease
GH	Gestational hypertension
HDL-C	High-density lipoprotein cholesterol
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
ICHD-3	International Classification of Headache Disorders 3
IL6	Interleukin-6
IR	Insulin resistance
MetS	Metabolic Syndrome
MI	Myocardial infarction
MM	Menstrual migraine
MRM	Menstrual-related migraine
PE	Preeclampsia
PFO	Patent foramen ovale
PMM	Pure menstrual migraine
POCs	Progestin-only contraceptives
SCAD	Spontaneous coronary artery dissection
SP	Substance P

TNF α	Tumor necrosis factor-α
TRPV1	Transient Receptor Potential Vanilloid 1
WC	Waist circumference

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