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REVIEW ARTICLE

Migraine during pregnancy and in the puerperium

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Abstract
Pregnancy can be seen as a positive time for women migraineurs because the elevated estrogen and endogenous opioid levels raise the pain threshold and the stable hormone levels, which no longer fluctuate, eliminate a major trigger factor for the attacks. In a great majority of cases, indeed, migraine symptoms spontaneously improve throughout pregnancy. Generally, migraine without aura (MO) improves better than migraine with aura (MA), which can occur ex novo in pregnancy more frequently than MO. After childbirth, the recurrence rate of migraine attacks increases, especially during the first month; breastfeeding exerts a protective effect against the reappearance of attacks. Migraine and pregnancy share a condition of hypercoagulability; therefore, attention must be paid to the risk of cardiovascular disorders, like venous thromboembolism and ischemic or hemorrhagic strokes. Some of these diseases can be linked to preeclampsia (PE), a serious complication of pregnancy, characterized by hypertension, proteinuria, or other findings of organ failure. This condition is more common in migraineurs compared with non-migraineurs; furthermore, women whose migraines worsen during pregnancy had a 13-fold higher risk of hypertensive disorders than those in which migraine remitted or improved. Pregnancy is generally recognized to exert a beneficial effect on migraine; nonetheless, clinicians should be on the alert for possible cardiovascular complications that appear to be more frequent in this patient population.

Keywords Cardiovascular risk · Migraine · Preeclampsia · Pregnancy · Puerperium

Introduction

Migraine is one of the most common benign neurologic illnesses, with an incidence of 18% among women and 6% among men [1]. Two primary forms are distinguished: migraine without aura (MO) and migraine with aura (MA) [2]. Frequent and intense attacks are extremely debilitating for headache sufferers, diminishing productivity and quality of life. Nonetheless, patients are often reluctant to seek diagnosis and treatment from a headache specialist, preferring instead to self-medicate while running the risk of chronicization of the disorder [3]. In women aged between 30 and 39 years—the central period of reproductive age—the incidence of migraine is 24% [1]. Among these women, the coincidence of pregnancy and history of migraine raise the risk of symptoms occurring during the pregnancy.

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We describe the course of migraine during pregnancy and the puerperium period, as well as the possible complications of migraine during pregnancy.

Epidemiology of migraine during pregnancy

There are two clinical reasons why pregnancy can be seen as a positive time for women migraineurs: the elevated estrogen and endogenous opioid levels raise the pain threshold and hormone levels no longer fluctuate, eliminating a major trigger factor that exacerbates attacks [4]. In 60–80% of cases, there is a spontaneous improvement in migraine symptoms throughout pregnancy, depending on the type of migraine and trimester of pregnancy [5].

a) Migraine without aura

In a sample of 47 women, MO more often than other types of migraine improved or remitted completely during the first trimester: general improvement in symptoms was reported in 46.8% and complete resolution in 10.6% [4]. Complete resolution was recorded in 53.2% during the second trimester, with a decrease in the average number of attacks from 2.4 ±

1.3 in the first trimester to 1.5 ± 1.5 in the second ($p = 0.002$). The remission rate during the third trimester was 78.7% (or 87.2% including symptom improvement without total remission of attacks). Some patients (10%) were attack-free during pregnancy and about 20% did not experience symptom improvement or reduction in attack frequency during the second and third trimesters (2.0 ± 2.1 vs. 1.4 ± 0.8) or attack duration (1.1 ± 0.2 vs. 1.0 ± 0.0 days in first vs. third trimester) despite a considerable reduction in attack intensity (2.5 ± 0.3 vs. 2.0 ± 0.0; $p = 0.001$) and use of analgesics (1.9 ± 0.7 vs. 1.2 ± 0.4 tablets; $p = 0.02$) compared with the first trimester.

At variance with the above-mentioned study, which did not observe worsening of migraine symptoms, Negro et al. [6] reported that MO worsened in 8% of cases but only during the first trimester, that it remitted or improved in 66.9%, and that it was unchanged compared with the period before pregnancy in 25.8% of cases. The authors explained that the lack of change in MO during pregnancy and the minor improvement of symptoms during the second and third trimesters were often correlated with an abnormal course of the pregnancy and the persistence of *hyperemesis gravidarum* (HG) during the second trimester, both of which are a source of anxiety and stress in patients. Migraine symptoms improved in over 50% of patients with HG only during the first trimester but did not resolve when it continued into the second trimester ($p = 0.0002$ vs. not having HG) [4].

The gradual improvement in migraine symptoms appears to follow the increase in endogenous blood levels of estrogen and progesterone during pregnancy, which is essential for its normal course. The increase in the plasma levels of progesterone and estradiol (20 and 30–40 times higher, respectively, than during the menstrual cycle) has a modulating effect on neurologic function during pregnancy [7].

Debate surrounds the association between the course of migraine during pregnancy and the presence of Menstrually Related Migraine (MRM) during the period before pregnancy. MRM occurs during the perimenstrual period (2 days before to 3 days after the start of menses) but also outside it [2]. According to some authors, a history of MRM should be considered a factor associated with poor improvement in migraine during pregnancy [4]; an improvement during the first trimester was seen in 40.7% of women with a history of MRM vs. 80% of women with non-Menstrual Migraine (nMM) and remission of migraine in the second and third trimesters (48.1% vs. 60.0% and 63% vs. 100%, respectively, MRM vs. nMM; $p = 0.005$).

Serva et al. [8] reported that a history of MRM is significantly associated with migraine attacks during the first trimester of pregnancy. Differently, Petrovski et al. [9] reported a higher remission rate and fewer migraine days per month in a group of patients with nMM as compared with a group with Menstrual Migraine (MM); however, the difference was not statistically significant during early pregnancy (17th week) or late pregnancy (32nd week) or the postpartum period (8 weeks after childbirth). The only statistically significant correlation was between attack intensity and history of irregular menses. Attack intensity during the 17th week was greater in women with MM than in those with nMM (7.02 ± 1.75 vs. 6.21 ± 1.90; $p = 0.008$). In the 1960s, Lance and Anthony [10] expressed a different opinion on the changes in migraine during pregnancy in women with MRM: 64% of women with MM vs. 48% with nMM improved ($p < 0.05$). Recent studies have confirmed these findings [11, 12].

Melhado et al. [13] found that the percentage of improvement (defined as a reduction of at least 50% in attack frequency or intensity or both) and remission in women with a history of MRM was greater than in those with nMM during pregnancy: 62.22% vs. 44.93% (first trimester); 74.17 vs. 51.63% (second trimester); and 77.78% vs. 54.90% (third trimester) ($p < 0.001$ for all comparisons) (Table 1). No significant association between the time of MRM onset and the changes in migraine during pregnancy was revealed. Differently, another study [15] showed greater improvement in migraine symptoms during pregnancy in women with MM that began at menarche than in those in which it began later.

There is little consensus on the difference in the course of MO in primiparous and multiparous women. Some studies [4, 16] found no significant difference between these two subgroups. Other studies reported worsening of migraine symptoms in subsequent pregnancies in about 50% of multiparous women [6], particularly if the attacks persisted in the first pregnancy [17]. The Head-HUNT study [18] showed, in women aged ≤ 40 years, a lower 1-year prevalence of migraine in primiparous women than in multiparous (odds ratio [OR] 0.6, 95% confidence interval [CI] 0.3–0.9 vs. OR 0.9, 95% CI 0.7–1.1). Scharff et al. reported a U-shaped curve for migraine during pregnancy in multiparous women, with worsening of symptoms at the end of the third trimester [19].

MO may occur ex novo during pregnancy in women without a history of the disorder. The estimated prevalence is about 10% [16] but was found to be higher (16.8%) according to an Internet survey [20] in which the occurrence of "definite migraines" (diagnosed according to the ID migraine test) did not distinguish between MO and MA.

b) Migraine with aura

MA tends to improve during pregnancy but not as much as MO. Granella et al. [21] reported improvement and remission of MA in 43.6% of patients vs. 76.8% of those with MO, no change in 48.7% vs. 22.2%, and worsening of symptoms in 7.7% vs. 1%. Other studies [6] reported a substantially similar clinical course for MA and MO (improvement in 68.4% vs. 66.9%, no change in 23.2% vs. 25.8%, and worsening in 8.4%

Table 1 Course of migraine during pregnancy in patients with previous Menstrually- Related Migraine (MRM), Menstrual Migraine (MM), and non-Menstrual Migraine (nMM)

Study (year)	Study design	Population	Attacks frequency (%)	Improvement or Remission (%)	Statistical significance
Lance and Anthony (1966) [10]	Retrospective	N = 120		MRM 64 nMM 48	p < 0.05
Ratinahirana et al. (1990) [11]	Retrospective	N = 116 MO = 90 MA = 26		MRM 86 nMM 60	p < 0.02
Sances et al. (2003) [4]	Prospective	N = 47 (MO)		I trimester MRM 40.7 nMM 80 II trimester MRM 48.1 nMM 60 III trimester MRM 63 nMM 100	 p = 0.005 p = 0.005 p = 0.005
Melhado (2005) [13]	Prospective	N = 993 MRM = 360 nMM = 612		I trimester MRM 62.22 nMM 44.93 II trimester MRM 74.17 nMM 51.63 III trimester MRM 77.78 nMM 54.90	 p < 0.001 p < 0.001 p < 0.001
Serva et al. (2011) [8]	Retrospective	N = 295 MO = 266 MA = 29	I trimester MRM (MO) 73.9 nMM (MO) 60.3 MRM (MA) 75 nMM (MA) 65.6		Adjusted PR 1.21 (95% CI 1.02-1.41) 1 Crude PR 1.14 (95% CI 0.85-1.54) 1
Hoshiyama et al. (2012) [27]	Prospective	N = 60 MRM = 20 nMM = 40		I trimester MRM 50 nMM 67.5 II trimester MRM 85 nMM 75 III trimester MRM 85 nMM 87.5	 NS NS NS
Petrovski et al. (2018) [9]	Prospective – longitudinal population-based	N = 280 MM = 52 nMM = 228		17 GA MM 3.8 nMM 7.1 (intensity of attacks MM 7.02±1.90 nMM 6.21±1.90) 32 GA MM 42.3 nMM 40.4 Postpartum (8 weeks) MM 13.7 nMM 16.5	 NS (p = 0.008) NS NS

PR Prevalence Ratio, *NS* Not Significant, *GA* weeks of Gestational Age

vs. 8%). However, the ex novo occurrence rate during pregnancy was higher for MA than for MO (14% vs. 10%), and often, it occurs in patients with a previous history of MO [22]. Furthermore, during pregnancy, completely new aura symptoms may appear [23] or aura may occur without subsequent migraine attack [24].

Epidemiology of migraine during the postpartum period

A hallmark event in the postpartum period is the drop in estradiol plasma levels immediately after childbirth and continuing for the next 12 h, with an over 95% reduction [25]. This period is also characterized by fatigue, low and poor sleep levels, anxiety about becoming a parent, and mental stress. These factors are associated with the frequent reappearance of migraine, also in patients who experienced a net improvement in or remission of it during pregnancy. Already within 72 h after childbirth, migraine reoccurs in about 4% of women; the recurrence rate increases to 30–40% during the first week and 50–60% during the first month [4, 6, 14, 16, 19, 26]. Goldzmidt [27] reported an incidence of 6.3% for MO and 1% for MA. The MIGRA study [16] reported an increase in migraine attacks in the initial postpartum period followed by a drop in frequency starting with week 5. The study reported a significant increase in attack intensity, mean duration, and mean number of analgesics taken compared with pregnancy [16]. Other studies reported that postpartum attack intensity was similar to that before pregnancy and was greater than that experienced during the third trimester of pregnancy [4, 6].

Data on migraine recurrence and intensity during the postpartum differ according to whether the mother breastfeeds or not. In fact, breastfeeding exerts a protective effect against migraine (Table 2). The regular secretion of prolactin during breastfeeding can inhibit ovulation, plasma fluctuation of estrogen levels, and menses. In women who breastfeed exclusively, ovulation returns about 27 weeks after childbirth, whereas it returns within about 6 weeks after childbirth in women who do not breastfeed [14, 29]. Furthermore, during breastfeeding, vasopressin and oxytocin levels rise. Their antinociceptive activity could exert a protective effect against migraine. In women who breastfeed, the Headache Index calculated for the first 3 months postpartum was similar to that for the second trimester of pregnancy [5, 28]. However, some studies [16, 28] found no significant difference in postpartum attack frequency between women who breastfeed and those who bottle feed (Table 2).

Other risk factors significant for postpartum migraine could be epidural anesthesia mistakes [4, 27] and personal or family history of migraine [30]. Studies disagree on whether multiparity and age over 30 years can be considered risk factors for postpartum migraine [4, 14, 27].

Link between migraine, vascular diseases, and pregnancy

Migraine and pregnancy share a condition of hypercoagulability (Fig. 1). Pregnancy is associated with a change in homeostasis, with an increase in levels of procoagulant factors and a decrease in anticoagulant factors and fibrinolysis [31–33]. The elevated estrogen levels in pregnancy stimulate the liver to produce coagulation factors and raise circulating cholesterol levels. Progesterone exerts a myorelaxant effect on vasculature, leading to increased venous dilation and stasis of blood flow [34].

Platelet count decreases probably due to hemodilution resulting from increased plasma volume and destruction, particularly during the second trimester [35]. In some cases, factors VII, VIII, X, XII, von Willebrand factor, thrombin, and fibrinogen increase during pregnancy by over 1000% [31, 36]. There is a progressive decrease in protein S and increase in resistance to activated protein C [37]. Fibrinolysis is reduced due to the reduced activity of tissue plasminogen activator (t-PA), which remains low until an hour after childbirth. This fall in t-PA activity results from an increase of up to threefold in plasminogen activator inhibitor-1 (PAI-1) and PAI-2 produced by the placenta [32, 38] and an increase in thrombin-activatable fibrinolysis inhibitor (TAFI).

Taken together, these changes raise the risk of cardiovascular disorders. The incidence of venous thromboembolism (VTE) resulting from pregnancy-induced venous stasis is 4–5 times higher (relative risk [RR] 4.29, 95% CI 3.49–5.22) during pregnancy [39]. The RR is evenly distributed across the three trimesters but 20–80 times higher during the puerperium [37, 40, 41]. Stroke during pregnancy is extremely rare: 4.3–210 events per 100,000 childbirths [42]. Though rarer than VTE, it carries a surplus of 30% in mortality rate (0.66/100,000 childbirths) and of 10% in morbidity rate [43].

Moreover, there are many conditions that can contribute to increasing the risk of vascular events. A revision of the Nationwide Inpatient Sample evaluated the risk factors associated with stroke during pregnancy: of the 2850 stroke cases reviewed, about 11% occurred during the antenatal period, 41% during childbirth, and 48% during the postpartum period. Furthermore, 27% were ischemic stroke, 25% hemorrhagic, 2% due to cerebral venous thrombosis, and 46% correlated with a specific pregnancy event. The incidence was 34.2/100,000 childbirths (95% CI 33.3–35.1). The identified risk factors included age ≥ 35 years (RR 2.0, 95% CI 1.4–2.7), Afro-American ethnic origin (RR 1.5, 95% CI 1.2–1.9), hypertension (RR 6.1, 95% CI 4.5–8.1), heart disease (RR 13.2, 95% CI 10.2–17.0), thrombophilia including a past history of thrombosis or the antiphospholipid syndrome (APS) (RR 16.0, 95% CI 9.4–27.2), sickle cell anemia (RR 9.1, 95% CI 3.7–22.2), sideropenic anemia (RR 1.9, 95% CI 1.5–2.4), thrombocytopenia (RR 6.0, 95% 1.5–24.1), systemic lupus erythematosus (RR 15.2, 95% CI 7.4–31.2), diabetes mellitus (RR 2.5, 95% CI 1.3–4.6), smoking (RR 1.9, 95% CI 1.2–2.8), and alcohol use (RR 2.3, 95% CI 1.3–4.6). Importantly, however, the condition not correlated with pregnancy that influenced the risk of stroke the greatest was a history of migraine (RR 16.9, 95% CI 9.7–29.5). Other conditions

Table 2 Course of migraine in postpartum in patients who breastfeed or bottle feed

Study (year)	Study design	Population	Mean migraine days per week	Recurrence after delivery (%)	Statistical significance
Marcus et al. (1999) [28]	Prospective	N = 45 Breastfeeding = 33	Data not shown	Data not shown	NS
Sances et al. (2003) [4]	Prospective	N = 47 (MO) Breastfeeding = 37 Bottle feeding = 10		1st week Breastfeeding 21.6 Bottle feeding 80.0 1st month Breastfeeding 43.2 Bottle feeding 100.0	$p < 0.001$ $p < 0.001$
Kvisvik et al. (2011) [16]	Prospective	N = 158 Breastfeeding = 149 Bottle feeding = 9	7th week Breastfeeding 0.1 Bottle feeding 0.4 All postpartum period (8th week)		$p < 0.001$ NS
Hoshiyama et al. (2012) [14]	Prospective	N = 60 Breastfeeding = 38 Bottle feeding = 22 N = 40 Breastfeeding = 24 Bottle feeding = 16		1st month Breastfeeding 50.0 Bottle feeding 86.4 3rd month Breastfeeding 65.8 Bottle feeding 90.9 6th month Breastfeeding 71.1 Bottle feeding 95.5 12th month Breastfeeding 91.7 Bottle feeding 81.3	$p < 0.05$ $p < 0.05$ $p < 0.05$ NS

NS, not significant

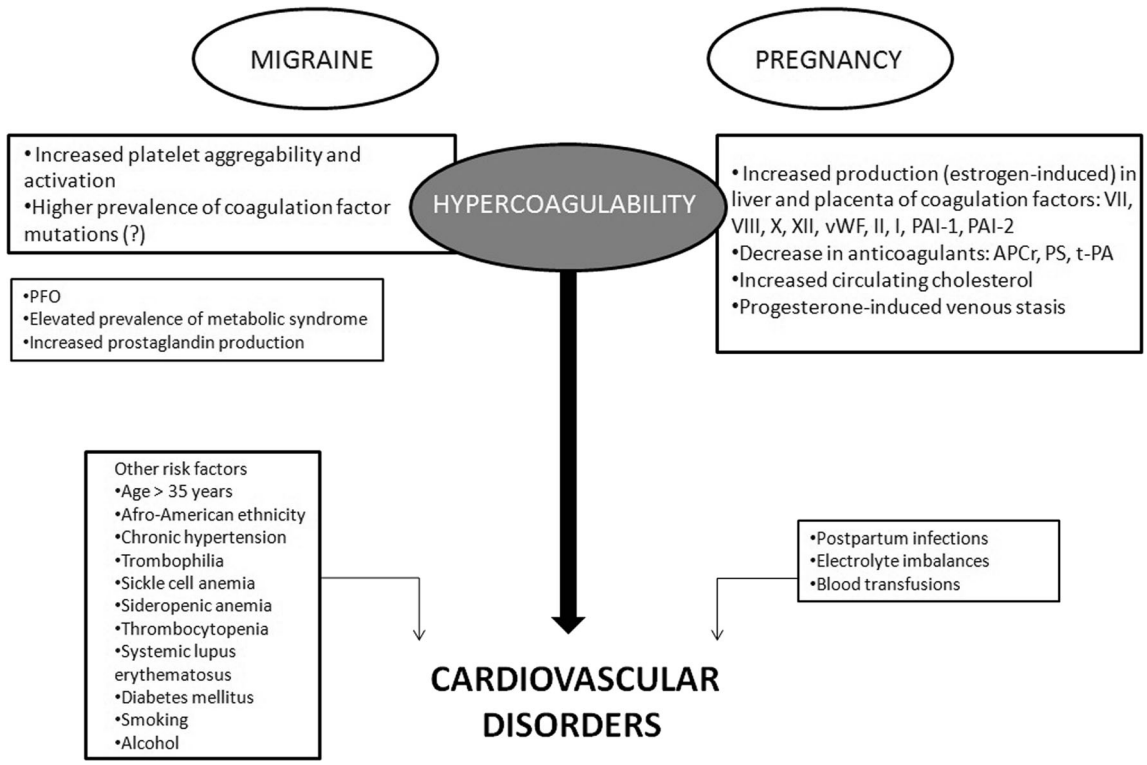

Fig. 1 Possible pathogenic mechanisms underlying cardiovascular disorders in pregnant migraine patients

correlated with pregnancy that raise the risk of stroke are pre-eclampsia (PE) (RR 4.4, 95% CI 3.6–5.4), postpartum infections (RR 25.0, 95% CI 18.3–34.0), electrolyte imbalances (RR 7.2, 95% CI 5.1–10.0), and blood transfusion (RR 10.3, 95% CI 7.1–15.1) [44].

Migraineurs are noted to have hypercoagulability, which could partly explain the increased risk of ischemic stroke, particularly in those with MA (OR 2.16, 95% CI 1.53–3.03) as compared with the general healthy population [45]. The increased aggregation and activation of the platelet pool [46] could result from increased expression of fibrinogen receptors [47] and glycoprotein IIb on the platelet surface [48]. ADP-mediated activation of the fibrinogen receptor is increased in migraineurs, as is the intracellular concentration of the two proteins [49]. In addition, receptor 5-HT is increased in number and function [50], as is the interaction between leukocytes, particularly polymorphonuclear leukocytes, and platelets [51]. The augmented expression of P-selectin on the platelet surface increases the adhesiveness of leukocytes and endothelial cells, especially during pain-free periods [52]. The release of thromboxane, oxygen free radicals, interleukins (IL1, IL6, IL8), and tumor necrosis factor α (TNF α) is increased [53]. Evaluation of a prothrombotic phenotype revealed increased levels of platelet factor 4 (PF-4), aspirin resistance [54], and a prevalence of antiphospholipid antibodies [55] which are known factors of vascular risk.

Analysis of mutation of coagulation factors in migraineurs has produced discordant results. Kontula et al. [56] found a strong association between Leiden factor V in post-stroke migraineurs; D'amico et al. [57] reported a decrease in activated protein C resistance and protein S in MA. These findings were not shared by other studies that found no difference in mutations in factor II, factor V, or factor VII between migraineurs and healthy subjects [58–60]. A recent case-control study compared migraineurs and healthy subjects to determine whether there were differences in the prevalence of Leiden factor V, protein C, protein S, antiphospholipid antibodies, and antithrombin III but found none [61]. The few studies that have investigated the presence of hyperhomocysteinemia as a risk factor for stroke in migraineurs have produced conflicting results. Hering-Hanit et al. studied 56 patients with MO and 22 with MA but found no difference in the prevalence of hyperhomocysteinemia as compared with 126 healthy controls [62], whereas D'Amico et al. reported a higher frequency of hyperhomocysteinemia among 109 migraineurs with MA as compared with 117 healthy controls [63]. The mechanism probably underlying hyperhomocysteinemia is a mutation in methylen-tetrahydrofolate reductase (MTHFR). Its polymorphism could be more frequent among migraineurs, particularly among those with MA [64, 65].

Although conclusive data are lacking, migraine, particularly MA, appears to be correlated with thrombocytosis and platelet hyperactivation, erythrocytosis, increased levels of von Willebrand factor, fibrinogen, and t-PA. There are conflicting data for the role of antiphospholipid antibodies, homocysteine, protein C and protein S, and MTHFR polymorphism [66].

In light of the above, women migraineurs are at increased risk of cardiovascular events during pregnancy due to their procoagulant state. Another condition that could explain this association is the presence of a patent foramen ovale (PFO), which is associated with cryptogenic stroke in young people and is found more often in women with MA. Given the lack of published data, the association between stroke during pregnancy in migraineurs and PFO is purely speculative [67]. Other factors to be considered include the presence of general risk factors for vascular disease. Migraine appears to be associated with a greater incidence of retinopathy and smaller diameter arterioles and venules [68]. An association between metabolic syndrome and migraine has also been hypothesized as patients present with high glucose and insulin levels, greater insulin resistance [69], and altered lipid profile [70]. Higher body mass index (BMI) also seems to predispose to chronicization of migraine [71, 72]. Augmented production of proinflammatory prostaglandins and thromboxanes in migraineurs [73, 74] may further alter a vascular endothelium that has already had to adapt to pregnancy.

Evaluation of the association between perinatal migraine and cardiovascular complications has shown an increased risk of ischemic stroke (OR 30.7, 95% CI 17.4–34.1), cerebral hemorrhage (OR 9.1, 95% CI 3.0–27.8), myocardial infarct (OR 4.9, 95% CI 1.7–14.2), VTE (OR 2.4, 95% CI 1.3–4.2), pulmonary embolism (OR 3.1, 95% CI 1.7–5.6), and thrombophilia (OR 3.6, 95% CI 2.1–6.1) [75]. However, these rates may be underestimated because based on the International Classification of Diseases, 9th revision (ICD-9), in fact, an estimated migraine incidence of 185/100,000 childbirths is far below than that estimated in women of reproductive age. Furthermore, the codes refer only to women hospitalized for active, severe migraine and do not include those with a history of migraine [67].

Migraine and hypertensive disorders of pregnancy

PE, a serious complication of pregnancy associated with increased risk of cerebrovascular events, may be a confounding factor in the evaluation of stroke risk among migraineurs during pregnancy. In symptomatic forms, patients complain of headache accompanied in some cases by scotomata and posterior reversible encephalopathy syndrome (PRES), one of the rare sequelae. However, PE may also be a predisposing factor for stroke. Indeed, studies have found an increased risk of PE in migraineurs, especially in those with worsening of migraine during pregnancy [67].

PE occurs in 3–7% of pregnancies and is universally defined as blood pressure $\geq$ 140 mmHg (systolic) and/or $\geq$ 90 mmHg (diastolic) on at least two measurements taken 4

to 6 h apart in a patient with previously normal values, associated with proteinuria ≥ 300 mg/24 h, after 20 weeks of gestation. Proteinuria absent, another finding of organ failure, must be present: platelet count < 100,000/μl, creatininemia > 1.1 mg/dl, twofold increase in liver transaminases, pulmonary edema, and neurologic signs or symptoms [76, 77].

Studies and literature reviews have documented a possible association between hypertension disorders in pregnancy and positive history of migraine (Table 3). However, the diagnosis of the two conditions did not follow standardized international criteria [67, 85, 94, 95]. In 2005, Facchinetti et al. [86] published a case-control study (150 women: 75 with a recent history of PE and 75 healthy controls) investigating migraine. Both migraine and PE were diagnosed according to internationally recognized criteria [96, 97]: 44% of the women suffered from headache, which was more prevalent among those with PE (47/75) than among the healthy controls (19/75) (OR 4.95, 95% CI 2.47–9.92). MO was more prevalent among women with PE, whereas tension-type headache (TTH) was equally present in both groups. Headache was more prevalent among women with severe PE than among those with mild PE (OR 5.63, 95% CI 1.97–16.03).

A multicenter, prospective study [88] interviewed 702 women between 11 and 16 weeks of gestation to diagnose the presence of migraine and to evaluate the outcome of pregnancy during the puerperium: 38.5% ($n = 270$) suffered from migraine (MO in 184, MA in 36, probable migraine in 50); hypertension developed in 5.2% ($n = 37$): gestational hypertension (GH) in 3.6%, and PE in 1.7%. The incidence of hypertension disorders was greater among migraineurs than non-migraineurs (9.1% vs. 3.1%); multivariate analysis showed an OR of 2.85 (95% CI 1.40–5.81). The incidence of hypertension was the same in women with MO and those with MA; the latter, however, were more numerous in the group that developed PE (5.9% vs. 2.9%). Women who experienced worsening of migraine during pregnancy had a 13-fold higher risk of hypertensive disorders than those in which migraine remitted or improved (OR 13.65, 95% CI 4.13–45.08). The low number of events precluded subanalysis of PE. The same study population was re-evaluated in 2012 [98] in an extended analysis of pregnancy outcomes and the impact TTH and migraine had on the outcomes: 38.6% of the women suffered from migraine and 15.1% from TTH. Pre-term delivery was more frequent among those with headache (OR 2.74, 95% CI 1.27–5.91). Subanalysis of women with migraine and those with TTH showed that TTH had a greater impact (OR 2.55 vs. 3.22). No correlation was found between headache and neonate born small for gestational age.

In their retrospective, case-control study comparing 339 women with PE and 336 with normal blood pressure, Sanchez et al. reported that a history of any type of headache was associated with a 2.4-fold higher risk of developing PE (OR 2.4, 95% CI 1.7–3.3). Women with a history of migraine before pregnancy had a 3.5-fold higher risk of PE (95% CI 2.2–5.4), while if migraine persisted into pregnancy, the risk increased fourfold (95% CI 1.9–8.2) as compared with women with normal blood pressure [87]. Another retrospective, case-control study published in 2010 [90] evaluated the prevalence of migraine in 180 women (90 with PE, 90 without PE) according to validated, standardized diagnostic criteria [96, 97, 99, 100]. Comparison between the two groups showed a nearly threefold higher risk of PE among the migraineurs (OR 2.87, 95% CI 2.33–3.1).

The correlation between migraine and PE could reside in their pathogenesis owing to the common features they share. Although not yet completely understood, the shared causal mechanisms are the altered endothelial reactivity and the abnormal release of systemic inflammatory mediators. Underlying PE is an altered trophoblastic invasion of the decidua, resulting in altered remodeling of the spiral arteries of the placenta. The resulting reduction in blood flow leads to local ischemic damage, with the release of inflammatory mediators and angiogenetic products (e.g., IL6, IL8, TNFα, vascular endothelial growth factor [VEGF], soluble fms-like tyrosine kinase 1 [sFlt-1], and endothelin) that produce systemic alterations in the endothelium. Other mediators that cause vascular damage are nitric oxide (NO), arachidonic acid metabolites, and the renin-angiotensin system. Since migraine is a neurovascular disorder, diverse neuropeptides and cytokines are implicated in its pathogenesis: calcitonin gene–related peptide (CGRP), IL6, IL8, and TNFα. Women who developed PE were noted to have elevated levels of adiponectin, which has anti-inflammatory activity, inhibiting inflammatory interleukins and TNFα and stimulating anti-inflammatory interleukins. Adiponectin levels are altered during migraine attacks [90].

Endothelin 1, a mediator of vasoconstriction and oxidative stress, is elevated in PE and migraine. Women with PE have elevated sensitivity to angiotensin; antibodies against angiotensin receptors can be found in some patients. Angiotensin receptor inhibitors can provide adequate migraine prophylaxis in certain cases [90].

Nocturnal secretion of melatonin is altered in MA, MO, and cluster headache [101]. Lower serum levels of melatonin and receptor expression in the placenta have been reported in women with PE [102].

Migraine attacks tend to diminish or remit during the second and third trimesters of pregnancy. This could be due to the more stable levels of estrogens and placental opioids. The lack of improvement or worsening of attacks, which is correlated with a high risk of PE, could result from a deficit in the production of estrogens and opioids by the placenta due to altered placentation. These aspects further underscore the importance of estrogen levels in the pathogenesis of migraine and in the maintenance of healthy endothelium. In non-migraineurs of reproductive age, endogenous estrogens exert a protective action against

Table 3 Risk of gestational hypertension (GH) and preeclampsia (PE) in women with migraine

Study (year)	Study design	Population	*Diagnostic criteria PE	**Diagnostic criteria migraine	Results
Rotton et al. (1959) [78]	Cross-sectional	221 hospital records	No	No	21.4% of migrainous pregnancies developed toxemia
Wainscott et al. (1978) [79]	Case-control	450 migraine, 136 controls, Headache clinic	No	No	18% of women in both groups reported a history of toxemia
Moore and Redman (1983) [80]	Case-control	24 PE, 48 controls, Hospital records	No	No	33% of case and 6% of controls reported migraine ($p < 0.01$)
Marcoux et al. (1992) [81]	Case-control	172 PE, 254 GH, 505 controls, Hospital records	No	No	aOR 2.44 (CI 95% 1.42–4.20) for PE aOR 1.70 (CI 95% 1.02–2.85) for GH
Chen and Leviton (1994) [82]	cohort	484 patients General population	No	No	21% of women with preexisting migraine developed toxemia
Chang et al. (1999) [83]	Case-control	291 stroke, 736 controls, Hospital	No	No	21% of migrainous women reported a history of high blood pressure in pregnancy. compared with 11% of non-migrainous women
Mattsson et al. (2003) [84]	Cross-sectional	728 patients, General population	No	No	aOR 1.26 (CI 95% 0.78–1.99) for GH and MO aOR 0.97 (CI 95% 0.38–2.13) for GH and MA
Scher et al. (2005) [70]	Case-control	482 migraine, 2517 controls, General population	No	Yes	aOR 1.63 (CI 95% 1.2–2.1) for GH
Adeney et al. (2005) [85]	Case-control	244 PE, 470 controls, Hospital	Yes	No	aOR 1.8 (CI 95% 1.1–2.7) for migraine
Facchinetti et al. (2005) [86]	Case-control	75 PE, 75 controls, Hospital	Yes	Yes	38.7% of cases and 10.7% of controls reported history of migraine ($p < 0.001$)
Sanchez et al. (2008) [87]	Case-control	339 women with PE, 337 controls, Hospital	Yes	Yes	OR 3.5 (CI 95% 2.2–5.4) for PE OR 4.0 (CI 95% 1.9–8.2) for PE if migraine during pregnancy
Bushnell et al. (2009) [75]	Case-control	18.345.538 pregnancy-related discharges (33.956 codes for migraine), Nationwide Inpatient sample	ICD 9	ICD 9	OR 2.3 (CI 95% 2.1–2.5) for PE(GH in migrainous women
Facchinetti et al. (2009) [88]	Prospective cohort	702 women (270 migraine)	Yes	Yes	aOR 2.85 (CI 95% 1.40-5.81) for PE/GH aOR 13.65 (CI 95% 4.13–45.08) for GH/PE if migraine worsened in pregnancy
Chen et al. (2010) [89]	Case-control	4911 women with migraine, 24.555 controls Nationwide population dataset	ICD-9	ICD-9	OR 1.34 (CI 95% 1.02–1.77) for PE in migrainous
Simbar et al. (2010) [90]	Case-control	90 women with PE 90 controls, Hospital	Yes	Yes	OR 2.87 (CI 95% 2.33–3.1) for PE in migrainous
Cripe et al. (2011) [91]	Prospective cohort	550 women with migraine Hospital	Yes	No	aOR 1.42 (CI 95% 1.00–2.01) for GH aOR 1.08 (CI 95% 0.55–2.15) for PE
Williams et al. (2011) [92]	Prospective cohort	3373 women (586 with migraine), Hospital	Yes	No	aOR 1.16 (CI 95% 0.71–1.91) for PE in lean women aOR 6.10 (CI 95% 3.82–9.75) for PE in overweight women
Czerwinski et al. (2012) [93]	Prospective cohort	3731 women (479 with migraine) Hospital	Yes	No	aOR 0.89 (CI 95% 0.49–1.63) for PE aOR 1.21 (CI 95% 0.85–1.74) for GH

*International Classification of Headache Disorders I, II, or III edition

**1996 ACOG diagnostic criteria, 2000 ACOG diagnostic criteria, 2000 National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (NHBPEP)

aOR, adjusted odds ratio

vascular damage, particularly against cerebral vascular injury, via their anti-inflammatory and immunomodulating activities. In vitro studies have shown that exposure to estrogens leads to a drop in the expression of NF-kB, iNOS, TNF, and IL1β, independent of genetic sex [103]; greater release of NO through the stimulation of endothelial synthesis; increased mitochondrial activity; and suppression of production of oxygen free radicals, in addition to a shift in the prostaglandin/thromboxane ratio in favor of the former [104]. These effects manifest clinically in the lower incidence of vascular disease in premenopausal women as compared with men and in a higher incidence of hypertension in postmenopausal women.

Conclusions

Women migraineurs require particular attention by all specialists caring for them during pregnancy. Pregnancy is generally recognized to exert a beneficial effect on migraine; nonetheless, clinicians should be on the alert for possible cardiovascular complications that appear to be more frequent in this patient population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This article does not contain any study with human subjects performed by any of the authors.

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