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Neurology of Preeclampsia and Related Disorders: an Update in Neuro-obstetrics

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Abstract

Purpose of Review—Preeclampsia and related hypertensive disorders of pregnancy affect up to 10% of pregnancies. Neurological complications are common and neurologists often become involved in the care of obstetric patients with preeclampsia. Here, we review the definition(s), epidemiology, clinical features, and pathophysiology of preeclampsia, focusing on maternal neurological complications and headache as a common presenting symptom of preeclampsia.

Recent Findings—Neurological symptoms are early and disease-defining features of preeclampsia. Neurological complications of preeclampsia may include headaches, visual symptoms, cerebral edema, seizures, or acute cerebrovascular disorders such as intracerebral hemorrhage or reversible cerebral vasoconstriction syndrome. A history of migraine is an independent risk factor for vascular diseases during pregnancy, including preeclampsia and maternal stroke. The pathophysiology of both preeclampsia and migraine is complex, and the mechanisms linking the two are not fully understood. Overlapping clinical and pathophysiological features of migraine and preeclampsia include inflammation, vascular endothelial dysfunction, and changes in vasoreactivity.

Summary—Neurological complications are recognized as a major contributor to maternal morbidity and mortality. Pregnant and postpartum women commonly present with headache, and red flags in the clinical history and examination should prompt urgent neuroimaging and laboratory evaluation. A focused headache history should be elicited from patients as part of routine obstetrical care to identify patients at an increased risk of preeclampsia and related hypertensive disorders of pregnancy. Collaborative models of care and scientific investigation in the emerging field of neuro-obstetrics have the common goal of reducing the risk of maternal neurological morbidity and mortality from preeclampsia.

Keywords

Preeclampsia; Neuro-obstetrics; Headache; Stroke; Maternal mortality

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Introduction

Preeclampsia and related hypertensive disorders of pregnancy are among the commonest of adverse pregnancy outcomes, affecting up to 10% of pregnancies in the USA [1]. Preeclampsia accounts for 6.9% of maternal mortality in the USA [2] and 14% worldwide [3]. Among women with preeclampsia, autopsy and detailed case series suggest that neurological complications are the direct cause of 30–70% of deaths, most often due to intracerebral hemorrhage or cerebral edema [4–7]. Despite this, unfortunately, neurological red flags in pregnant and particularly postpartum women are often missed. At least half of maternal deaths due to preeclampsia are thought to have been preventable with earlier recognition, diagnosis, and treatment [8–12].

The international obstetrics community now recognizes that neurological symptoms, including headache, can be disease-defining features of preeclampsia [13••, 14••]. However, the American College of Obstetricians and Gynecologists (ACOG) notes that "using headache as a diagnostic criterion for preeclampsia with severe features is unreliable and nonspecific" [13••]. Unsurprisingly, neurologists are frequently called to assist in the diagnostic evaluation of women who are being "ruled out" for preeclampsia. The diagnosis has major implications for blood pressure management, timing and mode of delivery, and discharge disposition. For this reason, it is critically important that neurologists understand the pathophysiology, clinical presentation, and neurological complications of preeclampsia and related disorders.

Here, we review the definitions, epidemiology, and complex pathophysiology of preeclampsia and related disorders as they affect the maternal brain, focusing on recent translational and clinical research findings. We discuss the relationship between migraine and preeclampsia, as well as the overlap between preeclampsia, the reversible cerebral vasoconstriction syndrome (RCVS), and the posterior reversible encephalopathy syndrome (PRES). Lastly, we discuss the evaluation of headache in pregnant and postpartum women at high risk for preeclampsia, focusing on headache features that should prompt escalation of care and involvement of a multidisciplinary neuro-obstetrics team.

Definitions and Epidemiology

Neurological Symptoms Are Early and Disease-Defining Features of Preeclampsia

Preeclampsia is a heterogeneous syndrome whose definition has evolved over centuries. However, headache and other neurological symptoms were recognized since the early days of medicine as a high-risk feature which can presage development of eclamptic seizures. Hippocrates noted in 400 BCE that "in pregnancy, the onset of drowsy headaches with heaviness is bad; such cases are perhaps liable to some sort of fits at the same time" [15], an apt description of eclampsia with prodromal neurological symptoms. Similarly, in 1843, Dr. Robert Johns of the Dublin Lying-In Hospital described a prodrome of "headache, weight, or giddiness in the head, ringing in the ears, [or] a temporary loss of vision… [In] most, if not all the cases… these very premonitory symptoms had been present before labour, and I argue, that had they attracted the requisite attention at that period, the subsequent convulsions might have been avoided" [16]. In 1994, Douglas and Redman reported that,

among 383 women with eclampsia, half reported headache prior to their convulsions, and 19% reported visual disturbances [17]. These symptoms often preceded the recognition or diagnosis of hypertension.

In 2013, ACOG re-defined preeclampsia, specifying that the disorder may be diagnosed in the absence of proteinuria, in women with new-onset hypertension after 20 weeks gestation together with evidence of other organ dysfunction, which includes neurological symptoms such as severe headache [18]. The International Society for the Study of Hypertension in Pregnancy similarly considers neurological features to be preeclampsia-defining when coupled with new hypertension [14••]. These features include severe headache, altered mental status, eclamptic seizures, stroke, persistent visual scotomata, or cortical blindness. Currently accepted diagnostic criteria for preeclampsia are detailed in Table 1, with neurological features highlighted. Neurologists must be familiar with these criteria, as the diagnosis has significant implications for management and disposition. Neurologists should also keep in mind that preeclampsia can occur in the postpartum period, as is discussed further in the following section.

Neuro-epidemiology of Preeclampsia and Related Disorders

Preeclampsia occurs in approximately 2–8% of pregnancies [13••]. Since many women have more than one pregnancy, the per-woman prevalence of preeclampsia may be substantially higher. A review of medical records from 9862 deliveries in Olmstead County, MN between 1976 and 1982 found that, while the incidence of hypertensive disorders of pregnancy and preeclampsia on a per-pregnancy basis was 7.3% and 3.5%, respectively, the incidence doubled when assessed on a per-woman basis [19]. Black, Indigenous, and women of color are disproportionally affected by preeclampsia as a result of systemic racism and structural inequities in healthcare [20, 21]. Preeclampsia rates are also far higher in low- and middle-income countries where access to prenatal care is limited [22]. Among women with chronic hypertension, up to 50% will develop superimposed preeclampsia [23].

Neurological complications seen in association with preeclampsia include seizures (eclampsia), arterial ischemic stroke, RCVS, PRES, cervical artery dissection, cerebral venous sinus thrombosis, subarachnoid hemorrhage (SAH), and intracerebral hemorrhage (ICH). Of these, ICH is the most devastating, directly causing up to 70% of deaths from preeclampsia [7]. While hemorrhagic strokes due to rupture of vascular lesions such as arteriovenous malformations and cerebral aneurysms have been reported in association with preeclampsia [24–27], there is often no underlying vascular lesion to account for the bleed [28]. Preeclampsia-associated maternal stroke has high morbidity and mortality. Half of strokes associated with hypertensive disorders of pregnancy are hemorrhagic [29] (for comparison, 87% of strokes are ischemic in the general population [30]), and 13% are fatal [29]. Stroke is associated with a 100-fold increase in mortality in women with hypertensive disorders of pregnancy [31].

Risk factors for neurovascular complications of preeclampsia include older age, non-white race, heart disease, chronic hypertension, infections, prothrombotic and hypercoagulable states, and history of migraine [29]. Migraine is associated with an increased risk of both

hypertensive disorders of pregnancy and maternal stroke [32••], an association which will be discussed further in the following sections.

Once thought to occur only in pregnancy and be cured by delivery of the placenta, it is now clear that preeclampsia and related disorders can occur in the postpartum period, including in women who had no history of gestational hypertension [33, 34]. In a study of 121 women with delayed-onset postpartum preeclampsia, 68% had headache as the presenting symptom [35]. In addition, antepartum diagnosis of, gestational hypertension or preeclampsia diagnosed antepartum can worsen after delivery and develop neurological sequelae, including eclamptic seizures [33]. In fact, the highest risk period for maternal stroke is postpartum [36], particularly in the first 2 weeks after delivery but with risk extending up to 12 weeks postpartum [28, 37•]. Furthermore, women with a history of preeclampsia have increased cardiovascular and stroke risk and earlier onset of clinical cardiovascular disease [38••, 39]. For this reason, a thorough obstetric history should be elicited from women presenting with cerebrovascular symptoms at any age.

Pathophysiology of Preeclampsia and the Maternal Brain

Pathophysiology of Preeclampsia

Like its definition, the cause of preeclampsia has been a subject of hot debate for decades, and a comprehensive discussion of its complex pathophysiology is beyond the scope of this review. The obsolete term “toxemia” reflects initial hypotheses that the syndrome was caused by a pregnancy-induced toxic or inflammatory state [40]. Subsequently, placental insufficiency or ischemia was recognized as a key factor in the pathogenesis of preeclampsia [41]. This is thought to occur due to poor implantation of the trophoblast, incomplete remodeling of spiral arteries in the placental decidua, or failure of the maternal cardiovascular system to meet the demands for increased cardiac output during pregnancy. Imbalance of angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), soluble endoglin, and placental growth factor (PlGF), leading to systemic maternal endothelial dysfunction, has been implicated in the pathogenesis of preeclampsia [42]. Several animal models of preeclampsia have been developed, including surgical models based on reduction of uterine perfusion pressure (RUPP), genetic models based on overexpression of sFlt-1, and environmentally induced models making use of inflammation-inducing infusions [43•]. More recently, the role of maternal inflammasomes expressed on the placenta has been recognized as a major contributor to the pathophysiology of preeclampsia. Inflammasomes are multiprotein signaling complexes composed of pattern recognition receptors and pro-inflammatory caspases, which are activated in response to danger-associated molecular patterns (DAMPs) and other stress- or pathogen-induced triggers [44]. The emergence of these innate inflammatory pathways as a key component of preeclampsia pathogenesis suggests that the perennial preeclampsia debate has come full circle back to the original “toxemia” hypothesis.

Preeclampsia and Cerebral Autoregulation

Cerebral autoregulation is the process by which cerebral arterioles react dynamically to changes in systemic blood pressure to ensure a constant flow of blood to the brain and

prevent hyperperfusion injury. Both animal and clinical studies have demonstrated impaired cerebral autoregulation in the preeclampsia syndrome [45•, 46, 47]. Impaired dynamic cerebral autoregulation was demonstrated in women with chronic hypertension and women with preeclampsia, but not in women with normal pregnancy or gestational hypertension [48, 49]. Another study showed paradoxically increased cerebral autoregulatory capacity in women with preeclampsia [50]. A study using a RUPP preeclampsia rat model found severely impaired autoregulation compared to controls [51•]. The same group later showed this effect to be associated with changes in the renin-angiotensin system [52]. However, another recent study showed paradoxically enhanced cerebral autoregulation in a preeclampsia rat model [53], and long-term autoregulatory dysfunction after preeclampsia was not seen in humans [54]. The complex relationship between cerebral autoregulation and preeclampsia is an area of active investigation.

Blood–Brain Barrier Dysfunction

Increased blood–brain barrier permeability has been demonstrated in several animal models of preeclampsia [51•, 55–57]. This impairment may account for the cerebral edema seen frequently in women with eclampsia and occasionally in women with preeclampsia, particularly those with neurological symptoms [58–61]. Radiographically, the pattern of edema shares some features with the posterior reversible encephalopathy syndrome (PRES) and is usually reversible if treated early and aggressively [62]. The mechanisms of blood–brain barrier dysfunction in preeclampsia are not fully understood but may be mediated in part by neuroinflammation [53, 63]. Preeclampsia is associated with elevations in serum markers of inflammation, including C-reactive protein, platelet and complement activation, and elevated pro-inflammatory cytokines including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-17 [64, 65]. Animal models have shown that TNF-α may play a critical role in preeclampsia-associated blood–brain barrier dysfunction [56]. Proteomic analyses of cerebrospinal fluid (CSF) from women with preeclampsia have shown clear differences compared with normotensive women, including increased markers of neuroinflammation and heme-binding proteins [66, 67]. Persistent cerebral edema and neuroinflammation were demonstrated several months postpartum in a RUPP rat model [68]. However, a recent study of women with and without preeclampsia did not show evidence of increased inflammatory markers in CSF from the preeclampsia group [69]. Preeclampsia also causes shedding of microvesicles from the stressed placenta into the maternal circulation, triggering a pro-inflammatory cascade due to recognition of DAMPs by maternal inflammasomes [70–72]. However, the effect of preeclampsia-associated alarmins and their receptors on neurovascular unit function in the maternal brain is not well understood. In addition, changes in angiogenic pathways likely play a role in preeclampsia-associated neurovascular unit dysfunction [56, 73, 74]. Bevacizumab, a monoclonal vascular endothelial growth factor (VEGF) inhibitor with a mechanism analogous to that of sFlt-1, has been shown to induce a preeclampsia-like state, including headache, cerebral edema, and seizures in nonpregnant humans [75, 76].

Hyperexcitability and Vasoconstriction

Preeclampsia is associated with increased sympathetic activity [77], hyperreflexia (no longer considered a defining feature), and, in the case of eclampsia, seizures. Preeclampsia's

very name indicates its status as a precursor to eclampsia, which is defined by new generalized seizures in the setting of preeclampsia. However, preeclampsia does not always lead to eclampsia, and eclamptic convulsions may occur with little to no preeclampsia prodrome. Pregnancy itself has been shown to increase seizure susceptibility [78•]. In the setting of cerebral hyperperfusion due to impaired autoregulation, as well as increased blood–brain barrier permeability, this may contribute to the development of eclampsia. The postpartum state, similar to sympathomimetic medications, is considered a vasoconstrictive trigger for RCVS [79•]. Magnesium infusion reduces the risk of seizures in women with preeclampsia; hypothesized mechanisms include NMDA receptor antagonism, blood–brain barrier stabilization, systemic vasodilation leading to rapid blood pressure reduction, and prevention or reversal of cerebral vasospasm [80, 81]. Interestingly, intravenous magnesium has been suggested as an effective treatment for both PRES [82, 83] and RCVS [84] outside of pregnancy, but this strategy has not been tested in a clinical trial.

Cerebral Small Vessel Disease

Preeclampsia is associated with a long-term increased risk of stroke [38••, 39] and cognitive impairment [85, 86]. The reasons for this may be complex, as preeclampsia and cerebrovascular disease share many risk factors. However, animal studies have demonstrated microvascular dysfunction as a direct effect of preeclampsia [45•]. Several studies have shown higher white matter hyperintensity volumes in women with a history of preeclampsia [87–90]. Whether preeclampsia directly causes long-term cerebral small vessel disease is an area of active investigation.

Migraine and Preeclampsia: Missing Links

Patients with migraine have an elevated risk of developing preeclampsia, with an odds ratio ranging from 1.08 to 3.5 [32••]. One retrospective case series of pregnant women with well-phenotyped migraine diagnoses showed a preeclampsia rate of 21.3%, fivefold higher than the risk in the general population; however, this study had no comparison group [91]. While migraine with aura is a known vascular risk factor in women [92], the risk of preeclampsia appears to be elevated in women with migraine regardless of the presence of aura. Women with active or frequent migraine attacks during pregnancy may represent a higher risk phenotype [93]. The connection between migraine and preeclampsia is not fully understood. While migraine is considered primarily a brain disorder, there is evidence that peripheral components, including trigeminal nerve afferents, dural immune cells, and vascular endothelial cells, play a major role in the pathophysiology of migraine pain [94]. The mechanisms that initiate migraine pain remain elusive and are likely complex and multifaceted. An overlap of neuroinflammation, vascular endothelial and smooth muscle cell dysfunction, platelet dysfunction, and changes in vascular reactivity may provide the link between migraine and preeclampsia (Fig. 1).

The headache phase of migraine is thought to involve sterile neurogenic inflammation, which leads to dural plasma protein extravasation and increased meningeal vascular permeability, arterial vasodilatation, and activation of local immune cells. Trigeminal nerve activation releases vasoactive neurotransmitters and neuropeptides, such as substance P

and calcitonin gene–related peptide, adjacent to meningeal blood vessels. These vasoactive neurotransmitters and neuropeptides, in turn, trigger meningeal arterial vasodilatation, dural plasma protein extravasation, and mast cell activation and degranulation [94]. Neurogenically mediated dural plasma protein extravasation following trigeminal ganglion stimulation has been demonstrated in animal models, and levels of the pro-inflammatory mast cell components TNF-α, IL-1β, IL-10, and histamine are increased during migraine attacks, supporting this hypothesis [95–97].

Factors outside of neurogenic inflammation likely also contribute to migraine pathogenesis. Genome-wide association studies have identified multiple genetic susceptibility loci that are independently associated with migraine. Most of the identified loci are involved in genes regulating vascular and smooth muscle tissues, suggesting that vascular and smooth muscle dysfunction plays a role in migraine [98]. The release of substances from the meningeal vascular endothelial and smooth muscle cells, such as endothelin-1, nitric oxide, pros-tacyclin, and IL-1β, may play a role in activating meningeal nociception in migraine [94].

The role of platelets in migraine remains disputed, and it is unclear if platelet dysfunction is a cause or a consequence of migraine pathophysiology. It has been shown that migraineurs have abnormalities in platelet membranes that lead to decreased membrane fluidity, increased platelet activation, and increased formation of platelet-platelet and platelet-leukocyte aggregates. Platelet-platelet aggregates may contribute to a prothrombotic tendency, and platelet-leukocyte aggregates are thought to stimulate the release of inflammatory mediators, such as IL-1, IL-6, IL-8, and TNF-α, which can promote sensitization and activation of meningeal nociceptors. Platelet activation also appears to lead to serotonin release from platelet dense granules and increase the activity of platelet nitric oxide synthase, which, in turn, can influence vascular reactivity [99].

Like migraine, preeclampsia is mediated, in part, by neuroinflammation, alterations in angiogenic pathways, endothelial cell dysfunction, changes in vascular reactivity, and blood–brain barrier dysfunction. Aberrant platelet activation has also been demonstrated as part of the preeclampsia syndrome, and inhibition of platelet activation with aspirin has been shown in randomized trials to reduce the risk of preterm preeclampsia [100, 101]. It is possible that patients with migraine have a genetically preexisting dysfunction of platelets, vascular endothelial cells, and smooth muscle cells, which makes cerebral and meningeal blood vessels more receptive to the neuroinflammation and the resultant increased blood–brain barrier permeability and vasoreactivity linked to preeclampsia. Decreased levels and impaired function of circulating endothelial progenitor cells have been demonstrated in both migraine [102] and preeclampsia [103, 104], suggesting an overlapping pathophysiology of vascular endothelial dysfunction. Increases in pro-inflammatory cytokines, such as TNF-α and IL-1β, and increased white matter hyperintensity volume identified in both migraine and preeclampsia support the idea that the two disorders may share similar pathways of neurovascular unit dysfunction and neuroinflammation. Given the risk inherent in migraine patients, a thorough headache and migraine history should be a standard part of obstetrical care to identify patients at an elevated risk of developing preeclampsia.

Clinical Considerations When Evaluating Pregnant and Postpartum Women with Headache

Migraine and tension-type headache are the most common primary headache disorders worldwide, contributing to more disability-adjusted life years than all other neurologic disorders combined [105, 106]. This burden is particularly high for young adult and middle-aged women, accounting for 11.2% of all years of life lived with disability in women between the ages of 15 and 49 according to the Global Burden of Disease Study 2016 [107]. Migraine is three times more common in women than in men, and women have the highest prevalence during their childbearing years, when up to 28% suffer from migraine [108]. Tension-type headache has a lifetime prevalence approaching 80% and has only a slight female predominance [109]. Tension-type headache is less influenced by pregnancy and has not been shown to increase the risk of hypertensive disorders of pregnancy [110•]. Migraine, on the other hand, is associated with an increased risk of vascular diseases during pregnancy, including gestational hypertension, preeclampsia, ischemic stroke, acute myocardial infarction and heart disease, and thromboembolic events [32••].

Headache is a common complaint leading to neurologic consultation, and an acute headache in a pregnant or postpartum patient is worrisome. Pregnancy and the puerperium itself are considered red flags that indicate a higher likelihood of diagnosing a secondary cause of headache [111]. While most pregnant patients presenting for neurologic consultation with an acute headache will have a primary headache disorder, more than one-third will be discovered to have an underlying secondary cause of their headache, the majority of which will be a hypertensive disorder of pregnancy [112, 113]. A recent retrospective study of postpartum patients requiring inpatient neurologic consultation for acute headache suggests even more reasons to be concerned in the puerperium, as 73% had a secondary headache disorder, most commonly postdural puncture headache (45.7%) and postpartum preeclampsia (26.1%) [114]. Other secondary headaches seen in pregnancy and the puerperium include headache due to cervical artery dissection (often associated with preeclampsia), RCVS, ischemic stroke (particularly in the posterior circulation), intracerebral or subarachnoid hemorrhage, and cerebral venous thrombosis.

Despite the heightened concern for secondary headache disorders, migraine and tension-type headache are the most common causes of headache during pregnancy [110•]. Large studies estimate that 67–89% of women will have a significant improvement in migraine attacks throughout pregnancy, most notably in the second and third trimesters [115]. Many women, however, will continue to have attacks throughout pregnancy. Migraine with aura is less likely to improve and more likely to start or worsen during pregnancy than migraine without aura. Patients who have migraine with aura may also develop new aura symptoms during pregnancy [110•]. Headache remains common in the puerperium, and up to 40% of women, regardless of migraine history, develop postpartum headache within the first week after delivery, largely resolving within 5 weeks. More than 75% of these postpartum headaches are primary headache disorders, and migraine can present for the first time in the postpartum period in 5% of patients [110•, 116, 117]. More than half of patients with migraine will

revert to their pre-pregnancy headache pattern within 1 month after delivery, a recurrence delayed only by breastfeeding and maternal age over 30 years [110•, 118].

Preeclampsia and related disorders make up the majority of secondary headache disorders in pregnancy. The headache of preeclampsia is often progressive and bilateral, pulsating in quality, intractable to treatment, and aggravated by physical activity. Patients can have associated visual changes, such as blurry vision and scotomas, which can be mistaken for symptoms of migraine aura [119]. PRES, a clinical-neuroradiological syndrome characterized by predominantly parietooccipital white matter lesions suggestive of vasogenic edema and various neurological symptoms, is often associated with preeclampsia and eclampsia [120]. Headache is the most common neurologic symptom in 2/3 of patients with PRES and eclampsia and generally is of insidious onset, dull quality, and bilateral occipital location [60]. RCVS is more common in the puerperium and presents as a sudden-onset (thunderclap), severe, diffuse headache that is recurrent over 1–2 weeks. Neuroimaging, which can be negative at headache onset, shows segmental cerebral vasoconstriction that starts at the periphery and progresses toward the central blood vessels and spontaneously resolves within 3 months [119, 121]. It can be difficult to differentiate the headache of preeclampsia and related disorders from migraine, as individual headache features are not significantly different and clinical features often overlap [114]. In patients with a history of a primary headache disorder, longer attack duration is suggestive of the diagnosis of a secondary headache disorder, whereas psychiatric comorbidity and phonophobia are more likely associated with a primary headache disorder [112].

Given the difficulty in distinguishing between primary and secondary headache disorders in pregnancy and the puerperium, a thorough history and examination, along with a high index of suspicion, are required. Red flags in the clinical history should prompt further neuroimaging and laboratory evaluation. Lack of headache history, elevated blood pressure, prior history of a secondary headache disorder, fever, very severe pain, and an abnormal neurological examination have all been found to be independent risk factors for secondary headache in pregnancy [112, 113, 122]. Laboratory evaluations associated with a secondary headache disorder in pregnancy include abnormal platelets, elevated C-reactive protein and liver function tests, proteinuria, and abnormal lumbar puncture results [123]. Independent risk factors for postpartum secondary headache disorders include lack of headache history, orthostatic headache, and abnormal neuroimaging [114].

When and How to Obtain Neuroimaging

Primary headache disorders, specifically migraine and tension-type headache, are highly prevalent in women of childbearing age. Even though most acute headaches in pregnancy and the puerperium will be a primary rather than a secondary headache, acute headache is one of the most common neurologic symptoms heralding preeclampsia. It can be difficult to distinguish between the headache of migraine and preeclampsia. Rapidly identifying headache features that should prompt emergent neuroimaging evaluation and early diagnosis and treatment is essential to reduce morbidity and mortality.

Various mnemonics have been proposed to describe red flag features of headache indicating a possible secondary cause. We propose the use of the mnemonic SCAN ME (Table

2) to help non-neurologists identify which pregnant and postpartum patients presenting with acute headache should be discussed with a neurologist and, in some cases, have urgent neuroimaging. We recognize this would be a significant change in practice from the current standard, and evidence to support this approach is lacking. Certainly, not all pregnant/postpartum women with severe headache require neuroimaging. However, given the potentially catastrophic consequences of missing a diagnosis (including the diagnosis of preeclampsia), in our opinion, decisions about neuroimaging are best made in collaboration with a neurologist if SCAN ME features are present.

Magnetic resonance imaging (MRI) is preferred over computed tomography (CT) only if immediately available, to avoid radiation exposure; however, fetal radiation from a maternal head CT is extremely low, and CT should be obtained if clinically necessary and MRI is unavailable or contraindicated [124•]. Gadolinium-based contrast should be avoided, as gadolinium crosses the placenta and has teratogenic and embryocidal effects in animal studies. While there are no well-controlled studies of iodine-based contrast agents in pregnant patients, animal studies have not demonstrated an increased risk from intravenous administration [124•]. If there is a suspicion for an acute cerebrovascular disorder, vascular imaging should not be delayed, and the fastest modality should be used [125••]. The American College of Radiology and ACOG both advise that iodinated contrast be administered during pregnancy, including the first trimester, when necessary to maternal care [124•].

Future Directions

Neuro-obstetrics as an Emerging Field of Scholarship and Clinical Practice

Neurological complications are recognized as a major contributor to maternal morbidity and mortality, and women commonly present with headache as the initial symptom. There is an urgent need for more basic, translational, clinical, and population-based research to better understand the mechanisms of preeclampsia-related neurotoxicity. Neurological disorders should be considered as both exposures and outcomes of interest in obstetrical clinical trials aimed at improving maternal health. In addition, neurologists and obstetricians must develop collaborative clinical care models to prevent, diagnose, and effectively treat the neurological complications of preeclampsia and related disorders. Obstetricians should elicit a focused headache history from patients at the first prenatal visit, and neurologists should incorporate a woman’s obstetrical history into their standard neurological consultations, particularly those for headache, cerebrovascular disorders, or cognitive complaints.

The term “neuro-obstetrics” has been introduced to describe this interdisciplinary care model [126]. Building on this, we propose that neuro-obstetrics be defined broadly as a cross-disciplinary field encompassing clinical practice, medical education, scientific investigation, and public health initiatives, with the overarching goal of reducing maternal neurological morbidity and mortality. Preventing neurological complications of preeclampsia and related hypertensive disorders must be a top priority in this emerging field. Other important areas in need of investigation include translational research to understand the mechanisms of the association between migraine and hypertensive disorders of pregnancy, identification of high-risk clinical features of migraine (such as aura status

or attack frequency by trimester), and the potential use of preeclampsia serum biomarkers to help rapidly assess acute headache in pregnancy where there is diagnostic uncertainty. Aspirin for preeclampsia prevention is already the standard of care for women with certain high-risk conditions [127]; the use of prophylactic aspirin in pregnant women with migraine could be investigated in clinical trials. Neurologists and neuroscientists can and should play central roles in identifying and closing the many knowledge gaps in this critically important area of neuromedicine.

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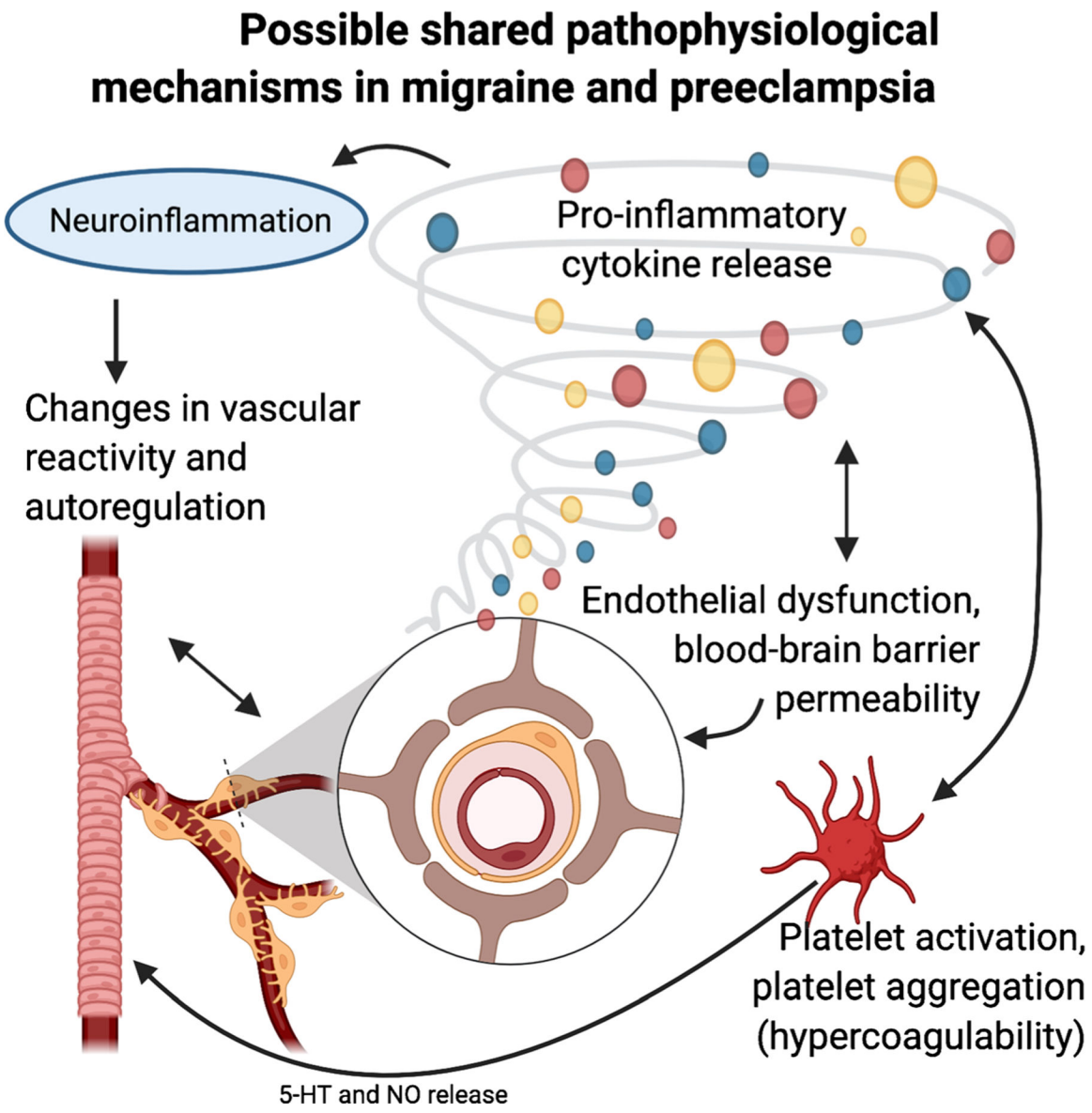

Fig. 1.

Possible shared pathophysiological mechanisms in migraine and preeclampsia. Preeclampsia and migraine share overlapping pathophysiology, including inflammation and endothelial dysfunction. Like migraine, the cerebral effects of preeclampsia include neuroinflammation, alterations in angiogenic pathways, endothelial cell dysfunction, changes in vascular reactivity, blood–brain barrier dysfunction, and platelet activation. This may account for the epidemiological association between migraine and risk of preeclampsia; however, the specific mechanisms of this association are not well understood. Figure created with BioRender.com

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Table 1

Defining characteristics of preeclampsia and related disorders

	ACOG (2019 revision)	ISSHP (2018 revision)
Preeclampsia		
New-onset, persistent hypertension at or after 20 weeks pregnancy in a woman with previously normal blood pressure AND	• SBP ≥ 140 mmHg or DBP ≥ 90 mmHg on two occasions at least 4 h apart, or • SBP of ≥ 160 mmHg or DBP ≥ 110 mmHg confirmed within a short interval (min)	
Proteinuria	• ≥ 300 per 24-h urine collection or • Protein/creatinine ratio of 0.3 mg/dL or more or • Urine dipstick reading of 2+ (if other quantitative methods unavailable)	
OR In absence of proteinuria	New onset of any of the following: • Thrombocytopenia • Renal insufficiency • Impaired liver function • Pulmonary edema • New-onset headache unresponsive to medication and not accounted for by alternative diagnoses, or visual symptoms	• Acute kidney injury • Liver involvement • Hematological complications (thrombocytopenia, DIC, or hemolysis) • Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth) • Neurological complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata)
Preeclampsia variants and related disorders		
Preeclampsia superimposed on chronic hypertension	• Preeclampsia in a woman diagnosed with chronic essential hypertension • New-onset thrombocytopenia, elevated liver transaminases, sudden development of symptoms suggestive of preeclampsia, or elevated uric acid levels suggest superimposed preeclampsia	• New-onset proteinuria or other maternal organ dysfunction in a woman with a diagnosis of chronic essential hypertension
HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets)	• LDH ≥ 600 IU/L • AST and ALT > twice the upper limit of normal • Platelet count < 100,000 × 10^9/L	• ISSHP does not define this as a separate condition and considers this condition to be part of the preeclampsia spectrum
Eclampsia	• **New-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions** (e.g., epilepsy, cerebral ischemia, intracranial hemorrhage, drug use)	• ISSHP does not define this as a separate condition and considers it a neurological complication of preeclampsia

Precise definitions of preeclampsia have been debated for decades. Note there are important differences between the ACOG and ISSHP definitions, **but both organizations consider severe headache or visual symptoms to be preeclampsia-defining in the setting of hypertension**. ACOG notes that women may not exhibit other signs of preeclampsia (e.g., hypertension, proteinuria) before presenting with seizures. Of note, **ISSHP also considers other neurological complications, including eclamptic seizures, stroke, altered mental status, and clonus, to be preeclampsia-defining in the setting of hypertension**

ACOG American College of Obstetricians and Gynecologists, *ISSHP* International Society for the Study of Hypertension in Pregnancy, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *LDH* lactate dehydrogenase, *DIC* disseminated intravascular coagulation

Table 2

SCAN ME: When to consider neuroimaging in a pregnant or postpartum patient with headache

S: Sudden/severe/seizure
C: Change in position (worse supine) or usual headache quality
A: Altered mental status
N: Neurological deficits/nausea and vomiting
M: Medications without relief
E: Elevated blood pressure or temperature

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