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Effects of the Menstrual Cycle on Neurological Disorders

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Abstract

Purpose of Review The menstrual cycle involves recurrent fluctuations in hormone levels and temperature via neuroendocrine feedback loops. This paper reviews the impact of the menstrual cycle on several common neurological conditions, including migraine, seizures, multiple sclerosis, stroke, and Parkinson's disease.

Recent Findings The ovarian steroid hormones, estrogen and progesterone, have protean effects on central nervous system functioning that can impact the likelihood, severity, and presentation of many neurological diseases. Hormonal therapies have been explored as a potential treatment for many neurological diseases with varying degrees of evidence and success. Neurological conditions also impact women's reproductive health, and the cessation of ovarian function with menopause may also alter the course of neurological diseases.

Summary Medication selection must consider hormonal effects on metabolism and the potential for adverse drug reactions related to menstruation, fertility, and pregnancy outcomes. Novel medications with selective affinity for hormonal receptors are desirable. Neurologists and gynecologists must collaborate to provide optimal care for women with neurological disorders.

Keywords Menstrual cycle · Menopause · Menstrual migraines · Catamenial epilepsy · Women's neurology · Ovarian hormones

Introduction

Understanding sex-specific influences on neurological diseases, such as the effect of the menstrual cycle, is important for optimal management. The hypothalamic-pituitary-ovarian axis controls the menstrual cycle. Gonadotropin-releasing hormone from the hypothalamic arcuate nucleus promotes follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release from the anterior pituitary. FSH and LH act upon the ovaries to stimulate estrogen and progesterone release, which exert feedback on the pituitary. The ovarian follicles mature in the first half of the menstrual cycle, the follicular phase, that leads to the release of the dominant follicle (ovulation) around mid-cycle, followed by the luteal phase when the corpus luteum produces progesterone. The fluctuations in ovarian hormones, temperature, and other variables associated with the female menstrual cycle can impact several neurological disorders (Fig. 1).

The International Classification of Headache Disorders 3rd Edition defines menstrual migraines as occurring between days −2 to +3 of the menstrual cycle, which are believed to be due to estrogen withdrawal.

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Migraine

Dutch physician Johannis van der Linden first described menstrual migraines inflicting a seventeenth-century noblewoman [1]. Migraine prevalence has a female to male ratio of three to one [2]. This gender disparity may owe to ovarian steroid hormone levels and fluctuations occurring during the female menstrual cycle. Migraine prevalence increases around the time of puberty and is most common among women of childbearing age, affecting an estimated 24% of women 30 to 39

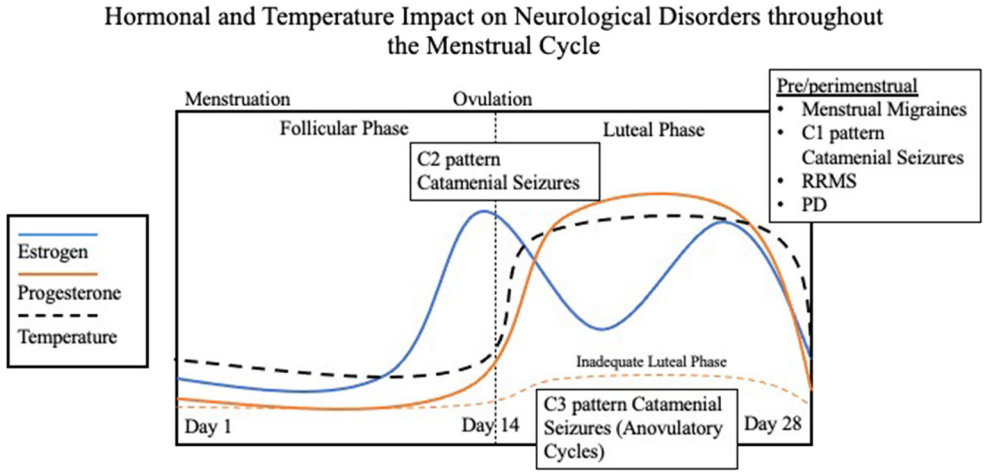

Fig. 1 The ovarian hormones, progesterone and estrogen, fluctuate throughout the menstrual cycle. Estrogen levels demonstrate bimodal peaks in the periovulatory and premenstrual phases. Progesterone is elevated during the luteal phase. Anovulatory cycles do not demonstrate the typical luteal phase progesterone elevation. Body temperature also fluctuates during the menstrual cycle with higher temperature throughout the luteal phase. Catamenial seizures occur in three patterns: C1 pattern is perimenstrual attributed to progesterone withdrawal, C2 pattern is periovulatory believed to be due to high estrogen-to-progesterone ratio, and C3 pattern occurs during the luteal phase of anovulatory cycles when progesterone remains low. Some women with relapsing–remitting multiple sclerosis (RRMS) experience symptom exacerbation during the premenstrual period, which may be due to the combination of declining estrogen and/or elevated body temperature. Parkinson's disease symptoms are also reported to be worse in the perimenstrual period and may be due to low estrogen levels

years of age [3, 4]. The International Classification of Headache Disorders 3rd Edition (ICHD-3) classifies pure menstrual migraine (PMM) as attacks occurring exclusively on day −2 to +3 of the menstrual cycle in at least two out of three cycles (day 1 is the first day of menstruation; there is no day 0). Women with menstrual-related migraine (MRM) may experience headaches at other times of the cycle in addition to days −2 to +3 [5]. ICHD-3 (in contrast with earlier iterations of the ICHD which limited the PMM and MRM diagnoses only for migraines without aura) now includes both migraines with and without aura. Menstrual migraines occurred in 22% of female migraineurs (and 7.6% of all women) of childbearing age in one population-based study. Migraines without aura occurred far more often than migraines with aura, and MRM was more common than PMM [6]. Menstrual migraine attacks may be more severe, painful, disabling, nausea provoking, longer lasting, and more likely to be associated with allodynia than nonmenstrual attacks [7–9]. A prospective headache and menstruation diary in addition to a detailed clinical history may assist in making the diagnosis [6].

The estrogen withdrawal hypothesis is a long-standing proposed mechanism for menstrual migraines [10]. Supporting evidence for this theory includes that many women have an improvement in their migraines during pregnancy, a time of rising and stabilizing estrogen levels, and subsequently experience recurrence of headaches in the early postpartum period when estrogen levels drop [11]. Migraine attacks more frequently occur during the hormone-free interval for women on combined oral contraceptives [12]. Two theories regarding the relationship between estrogen and migraines are the "magnitude of decline" and the "residual threshold." The magnitude of decline theory proposes that a minimum level of estrogen drop is needed to trigger a migraine attack, whereas the residual threshold theory posits a minimum blood level estrogen concentration that must be maintained to prevent migraine [13]. The rate of estrogen decline may also be relevant. In the Study of Women's Health Across the Nation (SWAN) Daily Hormone study, migraineurs had a comparable peak and mean estrogen levels but had a faster premenstrual decline in estrogen levels compared to healthy controls [14]. Other factors in the hormonal environment likely also contribute to menstrual migraines; however, the SWAN Daily Hormone study and earlier research found no obvious role for progesterone fluctuations contributing to migraines [14, 15]. However, other research suggests progesterone may downregulate estrogen receptors and reduce activation of trigeminovascular pain pathways [16]. Additional studies are required to identify other potential neuroendocrine factors related to menstrual migraines.

The association between the decrease in estrogen levels and headache may be mediated by several mechanisms. Estrogen receptors are located in many areas of the brain involved in processing pain, such as the thalamus, periaqueductal gray, amygdala, and trigeminovascular system [17]. Estrogen withdrawal may increase vascular susceptibility to prostaglandins, suppress endogenous opioid activity, act via serotonergic and dopaminergic effects, modulate neuronal excitability and pain perception, augment allodynia and central sensitization, and promote cortical spreading depression [18–20]. The release of calcitonin gene-related peptide

(CGRP) in the trigeminovascular system during an attack causes neurogenic vasodilation and nociceptive transmission, contributing to the migraine pathophysiology. Ovarian hormones, particularly estrogen, can modulate CGRP receptor synthesis, expression, and release in the peripheral and central nervous systems in a complex manner [21].

A successful treatment approach to menstrual migraines should target the pathways by which ovarian steroid hormones promote attacks. These treatments may be divided into hormonal and nonhormonal options. They can also be classified as abortive agents, short-term cyclic prevention, and daily prophylaxis. There are no US Food and Drug Administration (FDA)-approved medications specifically for menstrual migraines [20]. After Sommerville demonstrated in the 1970s that exogenous estradiol can delay the onset of menstrual migraines, others have investigated whether hormonal treatment may relieve menstrual migraines. Hormonal therapy may be an option for menstrual migraine without aura, although the fear of vascular events is a concern for patients that have traditional risk factors. Hormonal options tend to be more effective for PMM than MRM. (Notably, hormonal contraceptives can trigger or worsen headaches, defined in the ICHD-3 as headache attributed to exogenous hormones [5, 22].) The two main strategies for combined hormonal contraceptive treatment are low-dose estrogen during the menstrual week or extended duration hormonal contraceptives [13, 23–27]. For women with vascular risk factors for whom the use of combined hormonal contraceptives may have a greater risk, progesterone-only contraception may be an alternative to reduce the burden of menstrual migraines as well [28–30].

Limited data suggests that abortive migraine medications, including nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans, are less effective for menstrual than nonmenstrual attacks [31, 32]. Among the triptans, rizatriptan and sumatriptan led to greater than 60% efficacy in achieving a pain-free state at 2 h and were superior to placebo in clinical trials [33–35]. The combination of a triptan and an NSAID may be an effective abortive for menstrual migraines [36]. For women with regular menstrual cycles and predictable menstrual migraines, short-term cyclic prophylaxis in the perimenstrual period may be an effective treatment strategy [37]. One study showed an improved headache control with short-term frovatriptan as compared to transdermal estrogen or naproxen administration [38]. Perimenstrual use of NSAIDs remains a reasonable option for intermittent prophylaxis, particularly as they may improve both menstrual migraines and concomitant dysmenorrhea [39, 40].

CGRP receptor antagonists are a newer class of medication, which are effective against migraine headaches. Telcagepant, an oral CGRP inhibitor, when taken perimenstrually for 7 days reduced perimenstrual headaches but was associated with transaminitis [41]. The newer small molecule and monoclonal antibodies targeting CGRP have yet to be studied for menstrual migraine but may be promising therapeutics given the relationship between estrogen and this peptide [42, 43]. Vagus nerve stimulation and Botox injections are other potential treatments, but evidence in menstrual migraine is limited [44, 45].

Migraine headaches may also change with the onset of menopause. For many, menopause provokes an initial worsening of headache as estrogen levels fall, followed by sustained improvement [46, 47].

Seizures

Cyclical seizure exacerbations based on the phases of a woman's menstrual cycle define catamenial epilepsy. The exacerbations typically occur during the perimenstrual (C1 pattern) and/or periovulatory (C2) phase for ovulatory cycles; increased seizure frequency may occur during the luteal phase in anovulatory cycles (C3). An estimated 10 to 70% of women of reproductive age with epilepsy have catamenial seizures [48, 49•]. The prevalence varies greatly based on the population studied and the definition of catamenial epilepsy employed. One commonly employed definition is a twofold increase in seizure frequency above baseline [50]. Notably, the diagnosis is more challenging in women with irregular and/or anovulatory cycles, and data suggests women with mesial temporal sclerosis may be more likely to have anovulatory cycles [51]. A seizure diary tracking at least three menstrual cycles may assist in diagnosing the presence and pattern of catamenial epilepsy. A mid-luteal serum progesterone level is needed to confirm anovulatory cycles to help establish C3 pattern catamenial epilepsy with inadequate luteal phase. Catamenial epilepsy should be considered in the differential diagnosis for breakthrough and refractory seizures and assessed during history taking.

Fluctuations in ovarian steroid hormone levels, changes in antiepileptic drug levels, and other physiological changes likely contribute to catamenial epilepsy. In simplified terms, estrogen has a proconvulsant effect through increasing neuronal excitability, whereas progesterone has an anticonvulsant effect through enhancing GABA inhibition. A higher ratio of estrogen to progesterone lowers the seizure threshold. The premenstrual phase as progesterone levels rapidly fall and the periovulatory phase when estrogen levels rise rapidly are periods with lower seizure threshold in ovulatory cycles [51]. In anovulatory cycles, progesterone remains low during the luteal phase, leading to increased seizure tendency. Conversely, seizures are least likely to occur during the mid-luteal phase in ovulatory cycles, as progesterone levels are steadily high [52, 53].

Both ovarian steroids act via neurosteroid derivatives in the central nervous system. Circulating progesterone acts as a substrate for allopregnanolone synthesis [54]. Allopregnanolone acts as an allosteric agonist at GABA-A receptors and

influences GABA receptor subunit expression, thereby decreasing neuronal excitability. Progesterone administration has been shown to reduce ictal EEG activity in humans and to decrease seizures induced by GABA antagonists, drug withdrawal, and kindling in animal models. However, animal models and human studies of epilepsy suggest that the epileptic brain may be less sensitive to inhibition by neurosteroids, perhaps owing to NMDA receptor activation. Notably, a more dichotomous role of progesterone with antiepileptic acute effects, as described above, but also excitatory chronic effects via the progesterone receptor has recently been described and requires further investigation as it may impact potential therapeutics [55].

Estrogens enhance neuro-excitation via expression and activation of glutamatergic receptors and decrease neuroinhibition via suppressed GABA release [54, 56]. Estrogen administration increases seizure susceptibility in animal models, and higher levels of estrogen are positively correlated with seizure occurrence in women with epilepsy [57, 58]. However, estrogen's effects on the central nervous system are varied, and low doses may have neuroprotective effects [59, 60]. The precise role of estrogen in epileptogenesis needs further elucidation.

Catamenial seizures are often less responsive to traditional antiepileptic drugs and require a unique approach. Despite the evidence for the role of progesterone withdrawal in seizure provocation, an NIH-sponsored randomized clinical trial showed that progesterone for catamenial epilepsy was not superior to placebo [61]. An exploratory analysis suggests that progesterone may benefit women who had at least a threefold increase in seizure frequency in the perimenstrual period (strong C3 pattern) [62]. Hormonal therapy to induce amenorrhea has demonstrated possible benefit in small studies, although with concern for deleterious long-term effects [63, 64]. In contrast to menstrual migraine therapy, hormonal stabilization with contraceptives does not have sufficient evidence as an effective treatment for catamenial seizures [65]. Nonhormonal treatment strategies for catamenial epilepsy, in addition to standard antiepileptic dosing, include pulsed benzodiazepine and acetazolamide and augmentation of antiepileptic dosage prior to and during the period of seizure exacerbation [66–68]. These strategies have limited evidence and can only be employed with regular cycles. A 2019 Cochrane review concluded that the studies of hormonal therapy for catamenial epilepsy were underpowered, which highlights the insufficient data to guide both hormonal and nonhormonal treatment of catamenial epilepsy [69•].

Anti-seizure medication selection in women with catamenial epilepsy must also consider how hormone levels affect anti-seizure drug levels, the interactions between contraceptives and anti-seizure drugs, the teratogenic risks of anti-seizure medication, and other potential short- and long-term medication adverse effects.

Women with seizures are also more likely to have menstrual abnormalities, such as polycystic ovarian syndrome, and to have earlier menopause. Menstrual disorders may be due to a direct effect from epilepsy itself, as well as antiepileptic exposure, particularly valproic acid. Reproductive issues should be addressed in providing comprehensive care to women with epilepsy [70, 71].

The perimenopause period is characterized by increased anovulatory cycles with fewer cyclic progesterone elevations, coupled with erratic estrogen surges, which can increase seizure frequency in women with catamenial epilepsy initially. A sustained improvement usually follows as menopause completes [72–74].

Multiple Sclerosis

Variation in hormone levels can also impact chronic diseases, such as multiple sclerosis (MS), which presents as a relapsing–remitting and/or progressive disorder. Multiple sclerosis is an inflammatory demyelinating condition affecting the central nervous system, which is most prevalent in women of childbearing age [75]. Men tend to be diagnosed with MS at an older age and to have a primary progressive form, compared to women [76, 77]. The genetic, environmental, immunologic, and hormonal milieu contribute to sex differences in MS [78].

Women with MS may have worsening symptoms prior to menstruation. The deterioration is most reported among women with relapsing–remitting multiple sclerosis (RRMS) and likely results from both exacerbations (new demyelinating plaques) and pseudo-exacerbations (recrudescence of preexisting deficits due to prior plaques) [75, 78–81•]. In one study of cognition and physical performance, both women with and without MS demonstrated worse cognitive function in the premenstrual period compared with the periovulatory period, and MS patients had a decline in physical performance as well; additionally, women with MS had worse baseline measurements and greater premenstrual deterioration compared to healthy controls [81•].

Both body temperature variation and hormonal fluctuations are implicated in premenstrual worsening. Basal body temperature increases prior to ovulation and remains elevated throughout the luteal phase. The change may lead to a Uhthoff-like phenomenon (a worsening or recrudescence of neurological symptoms in demyelinating conditions due to an increased body temperature). However, temperature variation does not completely explain menstrual cycle symptom fluctuations [82]. The immunomodulatory and neuromodulatory effects of ovarian hormones also contribute to the pathophysiology of MS in women. For example, during pregnancy, in an immunomodulatory state with high levels of estrogen and progesterone, women with MS are less susceptible to exacerbations. A temporary

rebound with an increased risk of exacerbations occurs postpartum [83, 84•, 85]. A small prospective study reported worse MS symptoms among women taking combined oral contraceptives during the hormone-free interval [86]. How fluctuations in ovarian hormones during the menstrual cycle contribute to premenstrual symptom worsening is incompletely explained. A small study using serial imaging found the progesterone to estradiol ratio during the luteal phase correlated with the number and volume of enhancing lesions [87].

Due to the observed neuroprotective effect of some sex hormones, trials investigated if their use could augment MS therapeutics. In pilot and phase II clinical trials, oral estriol (an estrogen unique to pregnancy) as an add-on treatment in women with relapsing–remitting MS led to alterations in T cell populations and cytokine levels, which correlated with radiographic and clinical improvements [88–91]. Combined oral contraceptives also may provide anti-inflammatory and neuroprotective effects for women with RRMS when given in combination with disease-modifying therapies [92, 93]. However, data is limited, and the side effects of long-term exposure to estrogen remain a concern [94]. Progesterone is also thought to have anti-inflammatory and pro-myelinating effects [95]; however, a randomized controlled trial using high-dose progestin (with low endometrial-protective estradiol doses) to prevent postpartum MS relapses did not demonstrate a protective effect [96•]. Notably, in male MS patients, testosterone administration has limited evidence as a potential therapeutic [97].

As with epilepsy, women with MS are also more likely to have irregular menses, which may be due to the disease and to medication effects. Research suggests the incidence of menstrual irregularities increases significantly following the onset of MS [98, 99]. Women with MS may also have more perimenstrual symptoms than healthy controls [99•]. Medication selection for women with MS should also consider menstrual and reproductive side effects, including the potential for rebound exacerbations if disease-modifying therapies need to be held prior to pregnancy [84•].

The loss of ovarian function associated with menopause tends to be associated with accelerating disability and shift from relapsing–remitting towards progressive disease for women with MS [100•, 101]. Hormone replacement therapy with exogenous estrogens may improve quality of life but carries the risk of cardiac, thrombotic, and carcinogenic effects [102]. Selective estrogen receptor modulators (SERMs) are a potential future therapy to address MS and menopausal symptoms, although whether the neuroprotective effect is mediated via estrogen receptors is debated [103–105].

Parkinson's Disease

Hormonal variations also impact women with movement disorders. Parkinson's disease is a neurodegenerative condition affecting nigrostriatal dopamine transmission resulting in motor symptoms (bradykinesia, rigidity, tremor, postural instability), nonmotor symptoms (cognitive, psychiatric, autonomic), and systemic symptoms, which has many sex-related differences [106]. While PD is uncommon among menstruating women given the typical age of onset and male predominance, perimenstrual exacerbations of parkinsonian symptoms are reported in case series [107–110]. The periodic worsening may owe to estrogenic effects on the nigrostriatal dopaminergic pathways. The Parkinson's Disease on Estrogen Therapy Replacement (ERT) in the Menopause Years (POETRY) study was a small randomized controlled trial of ERT in postmenopausal women, which found a significant improvement in the Unified Parkinson's Disease Rating Scale with estrogen supplementation versus placebo [111]. Furthermore, according to a recent meta-analysis, menopausal ERT may reduce the risk of developing PD but this remains controversial [112, 113]. Hormonal therapy for the prevention or treatment of PD in premenopausal and postmenopausal women is not well established.

The premenstrual clinical worsening is also reported for some women with dystonia (a heterogeneous group of hyperkinetic movement disorders characterized by involuntary muscle contractions, twisting, and abnormal postures), and one may suspect other movement disorders could display menstrual fluctuations given the interplay between estrogen and the dopaminergic system [114, 115].

Estrogen impacts dopaminergic pathways at multiple levels, including synthesis, release, and reuptake and dopamine receptor expression in the basal ganglia. The effects vary with chronic versus acute exposure and with cyclic variation, such as occurs throughout the menstrual cycle [116]. Estrogen appears in some circumstances to be neuroprotective, but further understanding is required to develop hormonal therapeutics for women with movement disorders.

Stroke

Unlike the neurological conditions discussed previously, stroke risk and stroke phenomenology are not known to fluctuate within the menstrual cycle. However, menstruation, menopause, and hormonal therapies do impact stroke risk.

Women with irregular menstrual cycles may be at an increased lifetime risk of stroke, although metabolic abnormalities likely serve as an effect modifier [117]. Additionally, early age of menarche and premature menopause have been linked to increased risk of ischemic stroke, but the data is inconsistent [118–121].

Prior studies demonstrated an increased stroke risk in women taking combined oral contraceptives [122]. In clinical practice, women who have suffered an ischemic stroke are often counseled to avoid contraception with systemic estrogen, but they should be offered alternative birth control options given

the increased risk of stroke during pregnancy and should meet with a high-risk obstetrician for preconception counseling if pregnancy is desired [123].

Beginning in the perimenopausal period, women have escalating stroke risks [124]. Therefore, the loss of ovarian function, particularly estrogen, has been previously proposed as a stroke risk factor. Animal studies also suggested a neuroprotective role for ovarian hormones, which oophorectomy negated [125]. However, the use of hormone replacement therapy (HRT) in postmenopausal women has yielded disappointing results. The Women's Estrogen for Stroke Trial and Heart and Estrogen–Progestin Replacement Study failed to show any stroke reduction benefit from HRT [126, 127]. Furthermore, the Women's Health Initiative (WHI) study showed that exogenous estrogen actually increased the risk of stroke among postmenopausal women [128]. The link between estrogen and ischemic stroke may be complex and depend on age, timing, dose, and other factors [129]. Other hormones, such as LH and androgens, may link ovarian function, menopause, and stroke risk [130].

Several studies have found that women are less likely to receive thrombolysis for an acute stroke, although the reasons for this disparity are unclear [131, 132]. During early menstruation, fibrin and platelet aggregation may be altered and result in disturbed homeostasis. Although data on safety is limited, the benefit of thrombolysis therapy to treat disabling stroke likely outweighs the risk of increased uterine bleeding during menstruation and should not be a reason to defer treatment [133, 134].

Conclusions

Cyclic fluctuations in hormone levels and body temperature occurring with the menstrual cycle and menopause impact many neurological disorders. The premenstrual estrogen decline triggers migraine attacks due to estrogenic effects on prostaglandin, serotonergic, dopaminergic, and CGRP activity and changes in neuronal excitability, allodynia, central sensitization, pain perception, and cortical spreading depression. The progesterone decline in the premenstrual period and elevated estrogen to progesterone ratios in the periovulatory and inadequate luteal phases can predispose to seizure activity. Progesterone acts as an antiepileptic by increasing GABAergic activity, while estrogen is often epileptogenic via glutamatergic pathways. MS exacerbations and pseudo-exacerbations are more prevalent in the premenstrual phase due to increased temperature with declining estrogen likely contributing. PD and dystonia symptoms may worsen perimenstrually due to estrogen effects on dopaminergic activity.

A thorough obstetric and gynecological review of systems is an important component that should be emphasized during history taking for women with neurological disorders. An event and/or symptom log is often required to recognize catamenial patterns in neurological disease, particularly with irregular cycles, and to make a diagnosis.

Neurologists may be uncomfortable discussing women's health issues, and gynecologists may likewise be uncomfortable treating neurological diseases. Therefore, these two specialties should collaborate to optimally treat female neurological patients across the reproductive lifespan. A successful treatment approach includes consideration of hormonal therapy or cyclic dosing for predictable symptom exacerbation in women with regular menstrual cycles. Additionally, menstruation and reproductive health effects should be factored in for adequate medication selection.

Ongoing research must continue to uncover the pathways by which menstrual cycle fluctuations impact neurological disease and to investigate treatments designed to target these pathways. For example, new CGRP inhibitors are a promising option for menstrual migraines, and hormonal therapies should selectively act on estrogen and progesterone targets to maximize potential benefits and minimize hormonal side effects.

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