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Epilepsia®

CRITICAL REVIEW

Female sex steroids and epilepsy: Part 2. A practical and human focus on catamenial epilepsy

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Abstract

Catamenial epilepsy is the best described and most researched sex steroid-specific seizure exacerbation. Yet despite this there are no current evidence-based treatments, nor an accepted diagnostic tool. The best tool we currently have is tracking seizures over menstrual cycles; however, the reality of tracking seizures and menstrual cycles is fraught with challenges. In Part 1 of this two-part review, we outlined the often complex and reciprocal relationship between seizures and sex steroids. An adaptable means of tracking is required. In this review, we outline the extent and limitations of current knowledge on catamenial epilepsy. We use sample data to show how seizure exacerbations can be tracked in short/long and even irregular menstrual cycles. We describe how seizure severity, an often overlooked and underresearched form of catamenial seizure exacerbation, can also be tracked. Finally, given the lack of treatment options for females profoundly affected by catamenial epilepsy, Section 3 focuses on current methods and models for researching sex steroids and seizures as well as limitations and future directions. To permit more informative, mechanism-focused research in humans, the need for both a consistent classification of catamenial epilepsy and an objective biomarker is highlighted.

KEYWORDS

catamenial epilepsy, cycle tracking, menstrual cycle, seizure diaries, seizure exacerbation

1 | INTRODUCTION

The idea that seizures in women may be related to the menstrual cycle has been documented since 1881, when William Gowers reported a temporal relationship between seizure occurrence and menstruation in 46 of 82 women, with increased seizure frequency around menstruation.[1] Yet there is still some controversy and uncertainty about the prevalence of catamenial epilepsy, and it is still claimed that evidence for a hormonal cause of seizure cyclicity is inconclusive.[2-6] Several authors have even reported controversy around the existence of catamenial epilepsy at all.[7-10]

These controversies and uncertainties stem primarily from differences in the definition of catamenial epilepsy and the menstrual cycle phases in the clinical and scientific literature.[11] There is also the added complication that seizures display nonrandom cycles in general, including circadian, ultradian, lunar, multidien, and annual patterns and periodicities.[11] These complexities

lead to disagreement as to whether any association of seizure changes with the menstrual cycle is a subjective bias or spurious correlation that is driven by an acausal or separately mediated lunar/multidien cycle.[11] In the absence of an objective biomarker of catamenial epilepsy, the evidence of catamenial seizure exacerbation in an individual with epilepsy is subject to subject recall and reporting biases that are inherent in seizure diaries.[3-17] Nonetheless, Herzog[11] in particular, compellingly argued and demonstrated empirically that the existence of numerous cycles that impact seizures does not preclude the existence of catamenial seizure exacerbation.

When the cyclical nature of seizure frequency is tested independently of a priori hormonal considerations, seizure frequency appears to show a significant 28-day cyclicity in both ovulatory and anovulatory cycles, with the peak of seizure occurrence corresponding to the onset of menses.[10] Anovulatory cycles also showed significant 14-day and 9-day rhythms.[10] These findings lend support to (1) an intrinsic cyclicity of seizures that appears to be linked to the menstrual cycle onset, and (2) the existence of a different pattern of seizure exacerbation between ovulatory and anovulatory cycles.[11]

Key Points

- Catamenial epilepsy is the best documented and studied relationship between reproductive hormones and seizure frequency changes.
- There is a major lack of human research on catamenial epilepsy.
- Improvements can be made to seizure and menstrual cycle tracking from current methods; we show this using real examples.
- Our method allows for menstrual cycle irregularities within and between individuals; a method for tracking seizure intensity is also proposed.
- An objective biomarker of catamenial epilepsy in humans is needed.

2 | DEFINITION, DIAGNOSIS, AND PREVALENCE OF CATAMENIAL EPILEPSY

Catamenial epilepsy is typically identified by charting a diary of seizures and menses for a period of 3 months, and the number of seizures in each phase is counted,[9] although longer is better to rule out chance relationships between multidien and menstrual cycles.[5] Generally a catamenial diagnosis is given if seizure frequency increases by at least two-fold during a certain phase of the cycle in two of the three cycles.[9] A mid-luteal phase serum progesterone level is ideally obtained to distinguish between ovulatory and anovulatory cycles, with anything lower than 5 ng/mL indicating inadequate luteal phase.[18]

However, there is a wide variation in the degree of seizure exacerbation that is considered sufficient for a diagnosis of catamenial epilepsy (summarized in Table 1). Herzog et al.[18] defined catamenial epilepsy as an approximately two-fold increase in seizure frequency during the menstrual phase (days −3 to +3) compared to the mid-follicular (days 4–9) and mid-luteal phases (days −12 to −4), with day 1 being the first day of menstrual flow, and ovulation presumed to occur 14 days before the start of next menstruation (i.e., day −14). The authors also presented statistical evidence to support the existence of three distinct patterns of catamenial epilepsy: perimenstrual (C1: days −3 to 3) and periovulatory (C2: days 10 to −13) in ovulatory cycles, and inadequate luteal (C3: days 10 to 3) in anovulatory cycles (see Figure 1 for illustration). Later, Herzog et al.[9] clarified this and suggested that the specific increase in seizure frequency to make a diagnosis of catamenial epilepsy is specific to the subtype (C1: 1.69-fold, C2: 1.83-fold, and C3: 1.62-fold). These cutoff points are derived from multiples of average daily seizure frequency during the phase of exacerbation plotted relative to the comparator phase. These plots took on an S-shaped curve where the points of inflection distinguish women with high and low seizure sensitivity to cyclic hormonal changes and determine the cutoffs.

The prevalence of catamenial epilepsy among women with epilepsy varies widely depending on the diagnostic criteria.[11,19] Specifically, it has been reported that catamenial epilepsy affects anywhere from 10% to 70% of women with epilepsy.[20] Table 2 illustrates how the estimated percentage of women with epilepsy that will receive a diagnosis of C1 pattern varies according to 10 different cut-offs of seizure exacerbation.[11] For instance, approximately 6% of women will be diagnosed with C1 when using a 10-fold cut-off point, compared to 38% when using the recommended cut-off of 1.69-fold.

3 | ISSUES WITH CURRENT CRITERIA AND POSSIBLE SOLUTIONS

In addition to variations in diagnostic criteria, inconsistencies in the definition and treatment of menstrual cycle phases may all contribute to the considerable

TABLE 1 Summary of catamenial diagnostics criteria.

Authors	Diagnostic criteria	Phase definition
Newmark and Penry (1989)	Exclusively or predominantly during a 7-day period without specification of magnitude	Days −3 to +4
Duncan et al. (1993)	Having 75% of seizures during a 10-day period	Days −4 to +6
Herzog et al. (1997)	~2-fold increase during P compared to F, L, or both combined	P: days −3 to +3 F: days 4 to 9 O: days 10 to −13 L: days −12 to −4
Herzog et al. (2004)	Ratio of average daily seizure frequency during P relative to F and L equals or exceeds 1.69	P: days −3 to +3 F: days 4 to 9 O: days 10 to −13 L: days −12 to −4
Reddy (2007)	2-fold or greater during any phase of the cycle	P: days −3 to +3 F: days 4 to 9 O: days 10 to 16 L: days 17 to −4

Note: This table summarizes the different definitions of catamenial epilepsy by different authors.
Abbreviations: F, mid-follicular; L, mid-luteal; O, ovulatory; P, perimenstrual.

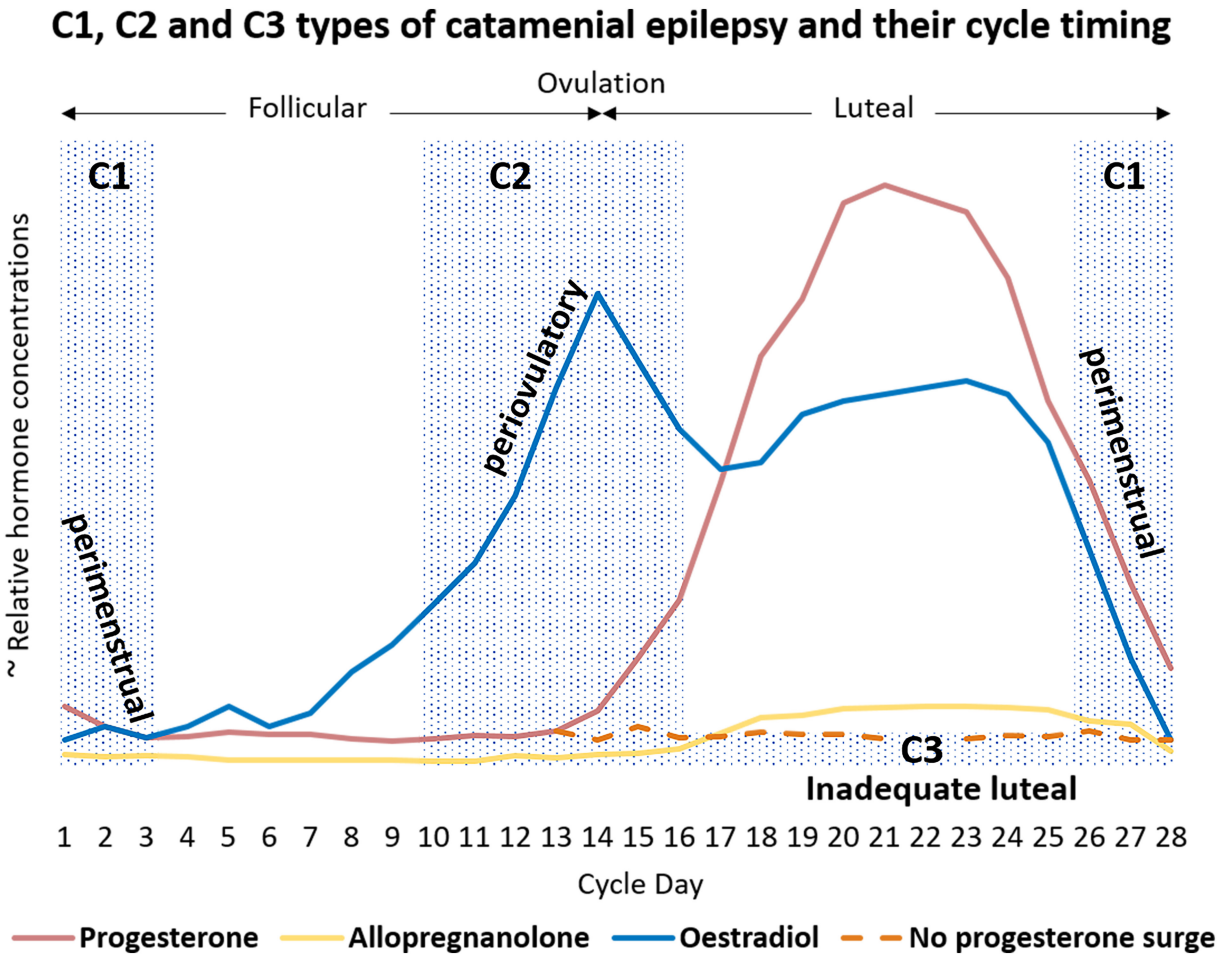

FIGURE 1 The temporal relationship between sex steroid fluctuations across the menstrual cycle and catamenial seizure exacerbation.

variation in the reported prevalence of catamenial epilepsy. For example, studies have excluded cycles shorter than 23 days or longer than 35 days[9] on the premise that menstrual cycle phase definitions become harder to estimate. This presents a major obstacle in representation and ecological validity, because women with epilepsy

TABLE 2 Table of data from Herzog[11] showing the relationship between the prevalence of perimenstrual seizure exacerbation (by percent of females with epilepsy) and defined seizure exacerbation threshold (as a ratio).

Ratio of seizure increase in perimenstrual phase	Females with epilepsy in sample, *n*	Females with epilepsy in sample, %
≥0	294	100
≥1	196	66.67
≥1.69[a]	112	38.10
≥2	101	34.35
≥3	63	21.43
≥4	51	17.35
≥5	44	14.97
≥6	36	12.24
≥7	31	10.54
≥8	24	8.16
≥9	22	7.48
≥10	19	6.46

Note: Data and table are from "Catamenial Epilepsy: Update on Prevalence, Pathophysiology and Treatment From the Findings of the NIH Progesterone Treatment Trial" by Herzog.[11]

[a]Herzog et al.[9] empirically determined cut-off ratio for classifying C1 (perimenstrual) catamenial epilepsy.

are known to often have abnormal variations in cycle length.[21] Further, in the context of randomized controlled trials, this is methodologically problematic, as it is likely to be a nonrandom criterion for excluding data. Existing methods tend to only report changes in seizure frequency. Although less often described, changes to seizure intensity are also an impactful form of catamenial seizure exacerbation.[22]

Thus, there is a clear need for a unified definition of catamenial epilepsy that is clinically relevant and applicable to all contexts in which catamenial exacerbation may occur, including short/long cycles. Below, we propose several solutions with examples from an existing cohort of patients with epilepsy (relevant ethics for publication of these data attained from the Health and Disability Ethics Committee, New Zealand; approval reference number: 21/CEN/201). We describe (1) how to deal with cycle length variability while retaining phase length invariability, (2) how to incorporate seizure intensity, (3) how to deal with perimenstrual seizures as the only seizures, and (4) how to classify C2 and C3 using our method.

It is important to note at this point that there are major issues with the accuracy of seizure diaries[12-15] that will be discussed further in Section 3. Ultimately, identifying a clinically useful objective biomarker that overcomes the limitations of seizure and menstrual cycle counting would be a major contribution to the field and clinic. However, in lieu of such a marker, improving the identification of catamenial seizure exacerbations is valuable.

3.1 | How to deal with cycle length variability while retaining phase length invariability

Although the "average" menstrual cycle is 28 days long, average variation includes cycles of 21–36 days.[23] This presents an issue when trying to define and even diagnose a disorder based on changes in seizures caused by different phases of the menstrual cycle, because the phases themselves do not lengthen and shorten proportionately to the cycle as a whole.

The variability in cycle length between women and from one cycle to the next is most often driven by varying lengths of the follicular phase.[24] The luteal phase is less likely to be lengthened/shortened than the follicular phase[23] and has a more constant duration of 14 days.[25] Ovulation is a relatively time-locked process. Estradiol increases, and when increased for 36 h, the gonadotropin surge is initiated and ovulation occurs 24 h later, making the preovulatory phase approximately 2–3 days long.[26] Progesterone is stimulated by the luteinizing hormone release, so it will also only begin to rise after the preovulatory phase and does so incrementally.[27,28]

Current methods for computing catamenial epilepsy do not universally allow for these constants. They only count back from the onset of menses by 12 (or 17) days to define the luteal phase, then count forward from the onset of menses 9 days to define the follicular phase. This does not allow the full length of the ovulation process to be allowed for and will only work for menstrual cycles that are longer

TABLE 3 Data from Bull et al.[30] showing follicular versus luteal length variability.

Cycle length (days)	Follicular phase length, mean days (±SD)	Luteal phase length, mean days (±SD)
15–20	10.4 (±2.4)	8.0 (±2.4)
21–24	12.4 (±2.2)	11.0 (±2.2)
25–30	15.2 (±2.5)	12.4 (±2.2)
31–35	19.5 (±2.7)	12.9 (±2.3)
36–50	26.8 (±4.5)	12.9 (±2.8)
All (10–90)	16.9 (±5.3)	12.4 (±2.4)

than 25 days before the preovulatory surge of estradiol starts overlapping with the follicular phase. Kim et al.[29] presented a simple solution in their study on catamenial epilepsy that we endorse and explain in further detail.

Backed by data from 600 000 menstrual cycles presented in Bull et al.[30] (Table 3), the solution is to adjust the length of the follicular phase only for cycles from 25 to 31 days and for long cycles. The perimenstrual phase (day −3 to +3), the ovulatory phase (counting 7 days backward from day −13), and the mid-luteal phase (−12 to −4) should be kept consistent across cycles and subjects. For precision, the luteal phase may be shortened to count back −11 days for shorter cycles (21–24 days long) and lengthened to −13 days for longer cycles (31 days long and over). For very short cycles (15–20 days long), the mid-luteal phase should be shortened to count back −8 days.

Using the above method, for long cycles, the average daily seizure frequency of the follicular phase will encompass all follicular seizures that occurred between the perimenstrual phase and the ovulatory phase. However, note that for 23-day cycles and shorter, when the luteal and ovulation phases are kept constant, only 1 day or even no days would remain as follicular (with the exception of 20-day cycles with 8-day luteal adjustment). This makes it impossible to calculate the average follicular daily seizure frequency, as it is entirely subsumed by the follicular portion of the perimenstrual classification. Thus, in these cases, we recommend that C1 should be thought of as an increase in seizure frequency or intensity during the perimenstrual phase compared to the luteal phase only.

Keeping the perimenstrual, ovulatory, and luteal phase length constant and varying the follicular phase prevents the exclusion of irregular cycles from catamenial epilepsy diagnosis and research. However, in addition to changing the phase partitioning for the calculation of seizure probability, it can be useful to normalize the cycle to 28 days to permit visualization and the averaging of cycles together. Having only adjusted the follicular phase, this can easily be calculated as:

$$\text{Average follicular daily seizure frequency} = \frac{\text{total number of follicular seizures}}{\text{corrected follicular phase length}} \quad (1)$$

An example of this being used and then plotted into graphs overlaying a single participant's seizures can be found in the Supporting Information, as well as in the examples below (Figures 2–5, Tables 4–7).

3.2 | How to incorporate seizure intensity

One example of use of seizure intensity in catamenial epilepsy classification is provided by Lim et al.,[22] who asked participants to rate seizures according to seizure duration, loss of consciousness, time to recovery to baseline, and self-injury. This type of reporting is quite burdensome for people with uncontrolled epilepsy, especially when experiencing several seizures a day. For our study, we have opted to use a 5-point scale where the ratings of participants individual seizure experiences are agreed upon with each participant. Examples include focal seizures being more intense and more noticeable because they were more likely to require engaging in intentional coping such as breathing through the aura and/or ictal phase compared to a small rush or tingle that does not stop participants. Alternatively, a stronger seizure rating may encompass changes to likelihood of generalized versus focal seizures or likelihood of focal seizures to evolve to bilateral seizures. What the ratings mean can be agreed upon between the participant and experimenter (or patient and clinician) and recorded in personalized instructions for the seizure diary with the aim being to make the defining characteristics of a stronger or weaker seizure as objective as possible.

Patient A reports a catamenial increase in severity of her seizures. She is unsure of a change in frequency. Patient A tracked her seizures for three full cycles over 103 days and rated their severity. Cycle lengths were 23, 56, and 24 days. To start with, we calculated changes to seizure frequency. The average follicular daily seizure frequency cannot be calculated for the first cycle (<23 days).

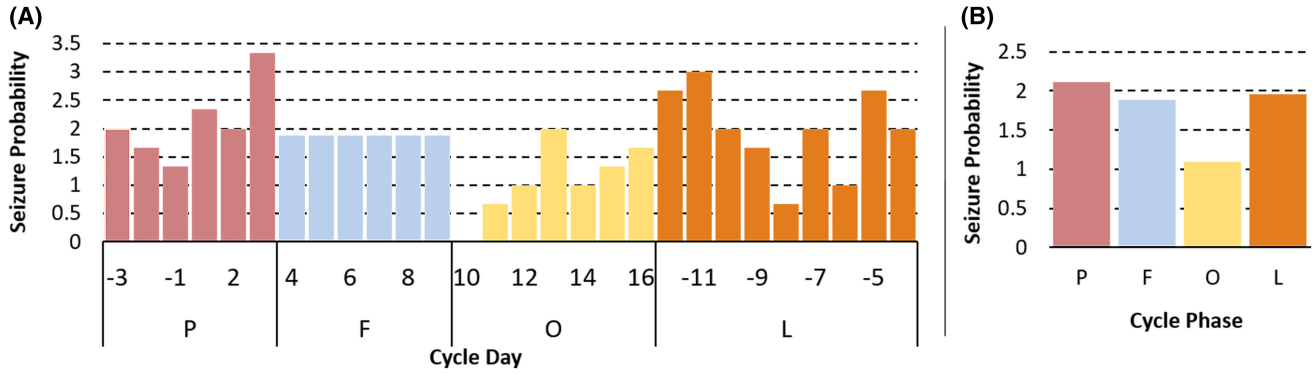

FIGURE 2 Average seizure frequency per day (A) and per phase (B). Data from Patient A comprise three full menstrual cycles over 103 days. There is no evident change in seizure frequency over the menstrual cycle, as corroborated by Table 4. Mid-follicular phase is normalized for illustration by computing average seizure probability (Equation 1) and superimposing it onto corrected follicular length. F, mid-follicular; L, mid-luteal; O, peri-ovulatory; P, peri-menstrual.

TABLE 4 Average daily seizure frequency across P, F, and L phases before and after normalizing follicular phase.

	Before normalization									After normalizing follicular					
					Herzog et al. 1997						Herzog et al. 1997				
Cycle	P	F	L	F + L	By F	By L	By F + L	Seizure ratio	Herzog et al. 2004	F	By F	By L	By F + L	Seizure ratio	Herzog et al. 2004
1	2.67	n/a	1.22	n/a	n/a	Y	n/a	2.18	Y	n/a	n/a	Y	n/a	2.18	Y
2	.83	2.14	3.22	5.37	N	N	N	.16	N	2.14	N	N	N	.16	N
3	2.83	1.5	1.44	2.94	N	N	N	1.46	N	1.5	N	N	N	1.46	N

Abbreviations: F, mid-follicular; L, mid-luteal; N, no; n/a, not applicable; P, perimenstrual; Y, yes.

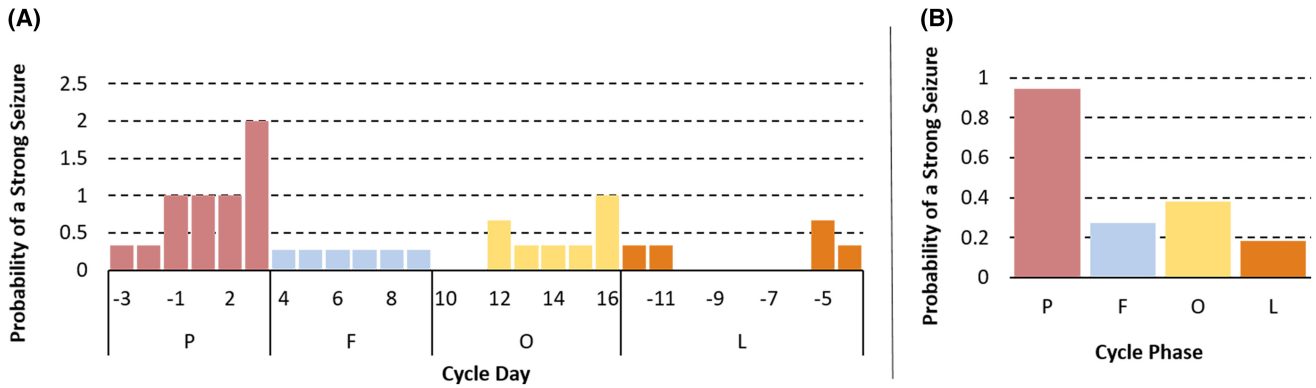

FIGURE 3 Average frequency of strong seizures per day (A) and per phase (B). Data from Patient A comprise three full menstrual cycles over 103 days. There is an evident increase in probability of a strong seizure in the perimenstrual phase, as corroborated by Table 5. Mid-follicular phase is normalized for illustration by computing average seizure probability (Equation 1) and superimposing it onto corrected follicular length. F, mid-follicular; L, mid-luteal; O, periovulatory; P, perimenstrual.

TABLE 5 Average seizure frequency across the P, F, and L phases, along with Herzog et al.[9,18] criteria for C1.

					Herzog et al. 1997				
Cycle	P	F	L	F + L	By F	By L	By F + L	Seizure ratio	Herzog et al. 2004
1	1	n/a	.33	n/a	n/a	Y	n/a	3	Y
2	.67	.82	0	.82	N	Y	N	.81	N
3	1.17	0	.22	.22	Y	Y	N	5.25	Y

Abbreviations: F, mid-follicular; L, mid-luteal; N, no; n/a, not applicable; P, perimenstrual; Y, yes.

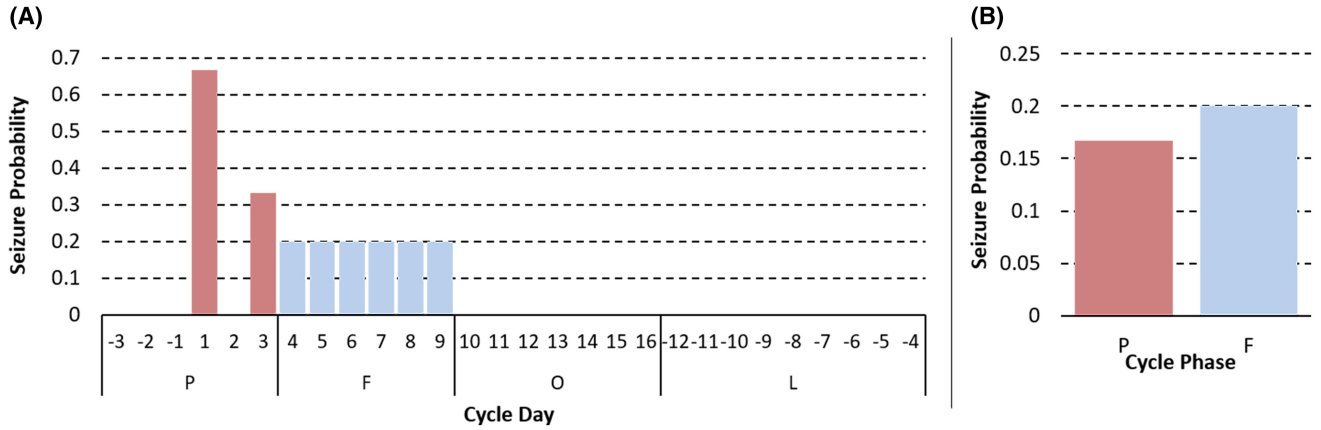

FIGURE 4 Average seizure frequency per day (A) and per phase (B). Data from Patient B comprise three full cycles across 83 days. Patient B only had seizures during the perimenstrual phase for two of three cycles tracked. Mid-follicular phase is normalized for illustration by computing average seizure probability (Equation 1) and superimposing it onto corrected follicular length. F, mid-follicular; L, mid-luteal; O, periovulatory; P, perimenstrual.

TABLE 6 Average seizure frequency across the P, F, and L phases, along with Herzog et al.[9,18] criteria for C1.

					Herzog et al. 1997					
Cycle	P	F	L	F+L	By F	By L	By F+L	Seizure ratio	Herzog et al. 2004	Our criteria
1	.17	0	0	0	N	N	N	1.33	N	Y
2	.17	0	0	0	N	N	N	1.33	N	Y
3	.17	.5	0	.5	N	N	N	.33	N	N

Abbreviations: F, mid-follicular; L, mid-luteal; N, no; P, perimenstrual; Y, yes.

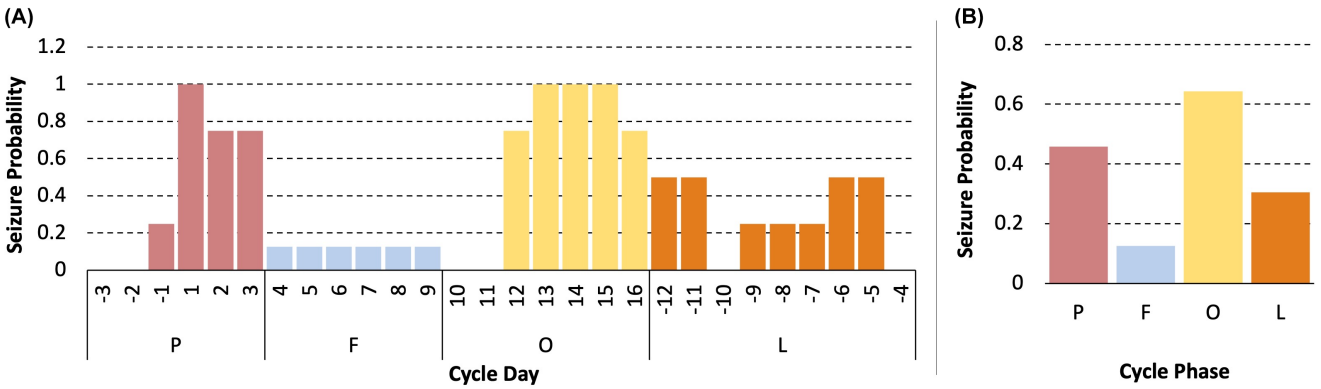

FIGURE 5 Average seizure frequency per day (A) and per phase (B). Data from Patient C comprise four full cycles across 95 days. There is evident exacerbation of seizures in the perimenstrual and periovulatory phases, as corroborated by Table 7. Mid-follicular phase is normalized for illustration by computing average seizure probability (Equation 1) and superimposing it onto corrected follicular length. F, mid-follicular; L, mid-luteal; O, periovulatory; P, perimenstrual. [Correction added on 8 March 2024, after first online publication: Figure 5 was updated to reflect the corrected data in Table 7.]

For the second and third cycles, the average follicular daily seizure frequency was the same before and after normalizing the follicular length, which demonstrates that normalizing follicular length to give a 28 day cycle is only needed for visualization purposes and for averaging or overlaying cycles (not used in calculation). Overall, this patient does not appear to meet the Herzog et al.[9,18] diagnostic criteria for C1 before or after normalizing follicular length (Table 4). This seems to align with a random distribution of the average daily seizure frequency (Figure 2).

To test for C1 as an increase in intensity for Patient A, we examined whether the frequency of strong seizures (seizures rated ≥ 2 out of 5 in a scale encompassing their usual mild sensation based focal to tonic clonic) showed

TABLE 7 Average seizure frequency across the P, F, O, and L phases, along with Herzog et al.[9-18] criteria for C2.

					Herzog et al. 1997 criteria				
P	F	O	L	F + L	By F	By L	By F + L	Seizure ratio (O relative to F + L)	Herzog et al. 2004 criteria
1	0	.43	.11	.11	Y	Y	Y	3.86	Y
.17	.5	1.14	.33	.83	Y	Y	Y	1.96	Y
.33	0	.86	.22	.22	Y	Y	Y	3.86	Y
.33	0	.14	.56	.55	Y	N	N	.25	N

Abbreviations: F, mid-follicular; L, mid-luteal; N, no; O, ovulatory; P, perimenstrual; Y, yes. [Correction added on 8 March 2024, after first online publication: In Table 7, the second row entry in the third column was updated from '.86' to '1.14' and the second row entry in the ninth column was updated from '1.03' to '1.96'.]

catamenial clustering. Using Herzog et al.,[9-18] we showed that this patient can be diagnosed with C1 by considering change in severity, because two of the three cycles met the diagnostic criteria (Table 5). This is also supported by the clustering of strong seizures during the perimenstrual phase (Figure 3).

3.3 | Dealing with perimenstrual seizures as the only seizures

Patient B tracked her seizures for three full cycles across 106 days. Her cycle lengths were 27, 29, and 27 days long. Herzog et al.[9-18] diagnostic criteria are not applicable in this case, because we cannot mathematically determine whether the average seizure frequency during perimenstrual phase (.17) is two times greater than that during mid-follicular or mid-luteal phase, as both are zero (Table 6). Similarly, a ratio of any number to zero cannot be calculated and thus treated mathematically. Although adding .5 to both sides resolves this issue mathematically, the resultant ratio (1.33) still does not meet Herzog's diagnostic cutoff of 1.69 (Table 6). This underestimates that the occurrence of a seizure during the perimenstrual phase compared to the absence of seizures during the rest of the cycle is, more or less, equivalent to 100% probability compared to 0%. This points to a significant limitation in automating or standardizing catamenial epilepsy classification using these methods, where both criteria fail to capture catamenial exacerbation when it manifests as an emergence of seizures during the perimenstrual phase. Furthermore, if we examined changes in average seizure frequency across the three cycles combined, that would also lend support to the absence of a catamenial pattern (Figure 4B). Thus, we recommend that cycles where perimenstrual seizures are the only seizures should be dealt with categorically (Did a seizure occur? Yes/No) to avoid obscuring catamenial patterns. According to our criteria, this patient would be diagnosed as having C1, because two of the three cycles showed perimenstrual emergence of seizures.

3.4 | Classifying C2 and C3 using our method

The empirically determined ratios of exacerbation for C2 and C3 type, as defined by Herzog,[11] are 1.83 and 1.62, respectively. Plotting the average daily seizure frequency of Patient C revealed a clustering of seizures during the perimenstrual phase and another clustering during the ovulatory phase, suggesting that Patient C might have C1 and C2 types (Figure 5). Applying Herzog et al.[9-18] criteria, Patient C could be diagnosed as having C2 type using either criterion (Table 7). This means that normalizing the follicular phase while keeping the lengths of the other cycle phases consistent is a potential diagnostic tool not only for C1 type but also C2.

C3 type exacerbation would also be simple to recognise using the principles introduced earlier. Noting that C3 type exacerbation occurs in the absence of progesterone surge during luteal phase and perimenstrual withdrawal thereof, there is no physiological justification to consider the perimenstrual phase separately. We propose that in this case the luteal phase should encompass (days -1 to -12), the ovulatory phase (counting 7 days backward from day -13), the follicular phase should include the rest of the cycle (and can be normalised to a 9-day period when required for visualization). For cycles shorter than 25 or longer than 31, the length of the luteal phase needs to be adjusted using the rules described above in Section 3.1. A C3 seizure exacerbation can therefore be calculated by comparing the luteal and ovulatory phases combined to the follicular phase.

C3 classification needs to be coupled with a blood test demonstrating high estradiol/progesterone ratio in the mid-luteal phase. This is said to most often occur with an inadequate luteal phase where progesterone ≤5 ng/ml is coupled with a rise in estradiol that may not be equivalent to a full luteal phase, but still produces a higher ratio than in a typical ovulatory cycle[11]. Though more burdensome for the patient, several blood samples that track early follicular, mid-follicular, luteal onset (or ovulation), mid-luteal phases provide the clearest picture, especially if menstrual cycle irregularity is also often experienced by the patient.

Patient D tracked her seizures for 3 full cycles across 139 days and underwent four blood tests during early follicular (day 3), mid-follicular (day 8), ovulation (day 16) and mid-luteal (day 21) phases. Plotting the average daily seizure frequency demonstrates a marked increase in seizure frequency during the luteal phase (Figure 6). This increase in seizure was coupled with diminished progesterone levels throughout the entire cycle, and a mid-luteal progesterone of 0.6 nmol/L which is the equivalent of 0.19 ng/ml that is well below the inadequate luteal proposed cut-off (Figure 7). Applying our proposed criteria for defining C3 and Herzog 2004 criteria demonstrate that patient D could be diagnosed with C3 type using either criterion (Table 8). Table 9 demonstrates that Patient D can also be diagnosed with C3 using Herzog 1997 et al criteria; however, we propose that it is more accurate not to consider the perimenstrual phase separately.

The exact concentrations of estradiol required or the threshold ratio of estradiol:progesterone are not yet defined empirically. Herzog[11] also mention that C3 may occur in ovulatory cycles if there is a high ratio of estradiol:progesterone in the luteal phase. Until an empirically determined ratio of estradiol:progesterone is determined, it will remain at the discretion of the researcher or clinician to decide whether to include ovulatory cycles in the classification of C3. It is interesting to note that in our case of Patient D, that no exacerbation appears to occur in the ovulatory phase (Figure 6), indicating a more complex role than pure estradiol concentrations and estradiol:progesterone ratio. C3 certainly warrants future research to ensure the full spectrum of

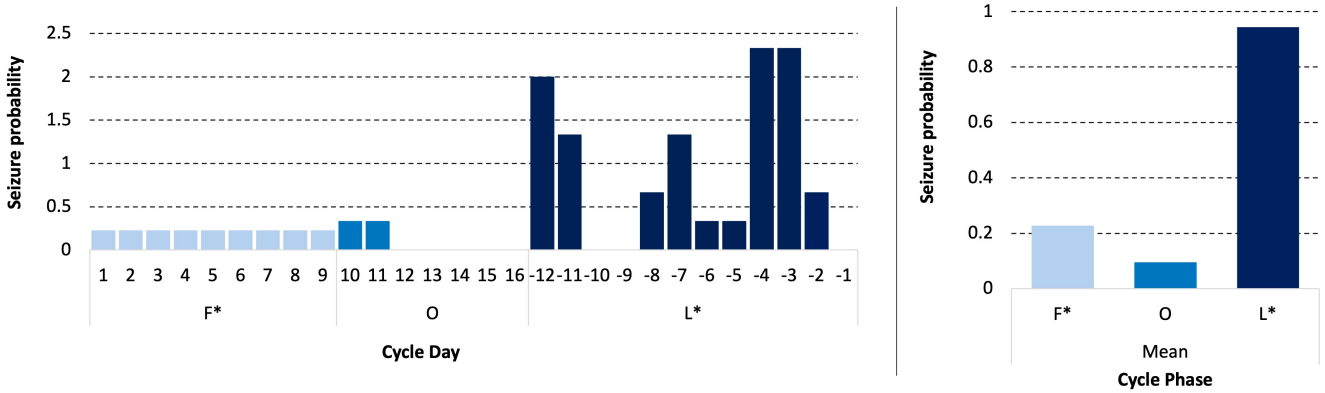

FIGURE 6 Average seizure frequency per day (A) and per phase (B). Data from Patient D comprises three full cycles across 139 days. There is evident exacerbation of seizures in the luteal (L) and ovulatory (O) phases compared to the follicular (F). This is corroborated by Table 8. Mid-follicular phase normalised for illustration by computing average seizure probability (Equation 1) and superimposing it onto corrected follicular length. Abbreviations: F*, Follicular; L*, Luteal; N, no; O, ovulatory; Y, yes.

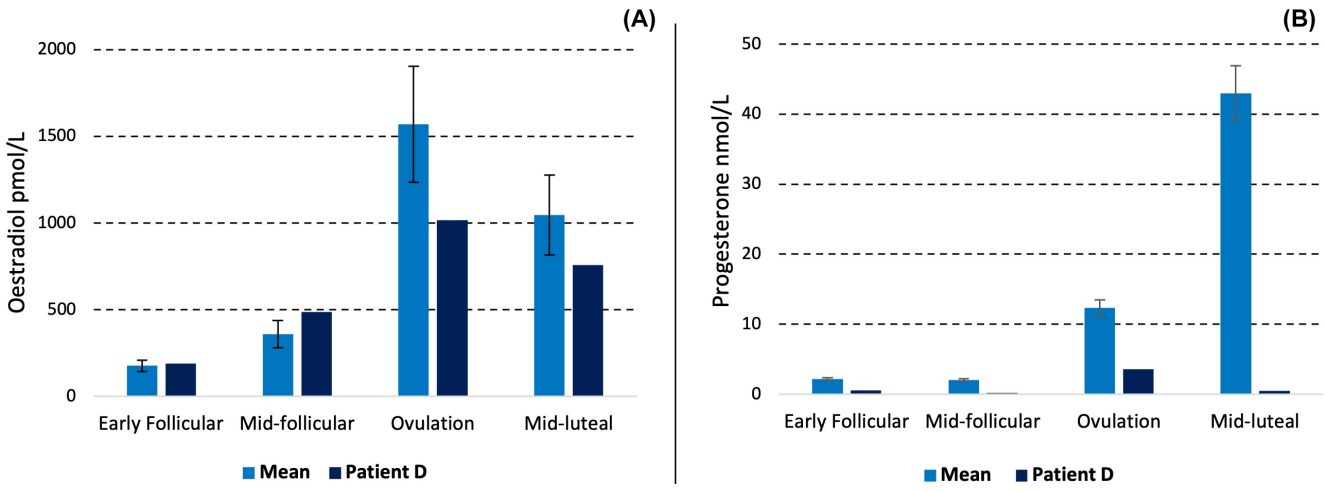

FIGURE 7 Patient D progesterone and estradiol levels on day 3 (early follicular), day 8 (mid-follicular), ovulation day and day 21 (mid-luteal) compared to the reference ranges for premenopausal women reported by Verdonk, Vesper[31] and Sundström-Poromaa, Comasco[32], respectively. Error bars represent standard errors.

Cycle	F*	O	L*	O + L*	Ratio (O and L* relative to F*)	Herzog 2004 criteria	Our criteria
1	0.37	0	1.33	1.33	3.63	Y	Y
2	0.15	0.12	0.83	0.98	6.51	Y	Y
3	0.17	0.14	0.67	0.81	4.86	Y	Y

Abbreviations: F*, follicular; L*, luteal; N, no; O, ovulatory; Y, yes.

TABLE 8 Average seizure frequency across the F*, O and L* phases, along with Herzog et al.[9,18] criteria for C2.

					Herzog 1997 Criteria			
Cycle	P	F	O	L	P + O + L	By P	By O	By L	P + O + L
1	0.33	0.33	0	1.11	1.44	N	N	Y	Y
2	1	0.16	0.14	1	2.14	Y	N	Y	Y
3	0.33	0.11	0.14	0.67	1.14	Y	N	Y	Y

Abbreviations: F, mid-follicular; L, mid-luteal; N, no; O, ovulatory; P, perimenstrual; Y, yes.

TABLE 9 Average seizure frequency across the P, F, O and L phases, along with Herzog et al.[9,18] criteria for C2.

catamenial seizure exacerbation is understood. Further, it may be difficult to distinguish C3 exacerbation pattern from a patient with combined C1 and C2 type. This distinction is important as it may indicate a different treatment approach is required based on differing pathophysiology (as suggested by the results of Herzog, Fowler[33]).

4 | STUDYING FEMALE SEX STEROIDS AND SEIZURES

The most prolific area of animal research into sex steroids and epilepsy is focused on the pathophysiology of catamenial epilepsy. Animal models of catamenial epilepsy can be categorized into three broad categories. The first two induce hormone changes and test seizure susceptibility. The first category attempts to mimic the luteal phase of the human menstrual cycle by inducing prolonged increased levels of progesterone and estrogens followed by an abrupt decline to mimic neurosteroid withdrawal during menstruation.[34] Examples of this category of models include the pseudopregnancy model[35] and the chronic exogenous progesterone model.[36] The latter assumes that exogenous chronic progesterone administration mimics the high progesterone levels during the luteal phase of the human menstrual cycle.[37] Although this might be true for progesterone and allopregnanolone (ALLO) levels, this model does not control estradiol levels and thus might not stimulate the changes in the progesterone-to-estradiol ratio that are believed to be critical in perimenstrual catamenial epilepsy.

The second category uses the naturally occurring estrous cycle, for example, by showing that the estrous cycle causes structural changes in extrasynaptic γ-aminobutyric acid type A ($GABA_A$) receptors.[38] Reddy[38] highlights this as a potential molecular mechanism that may be driving the decreased seizure susceptibility during the luteal phase.

The third category involves inducing epilepsy and then exposing the epileptic animals to steroid hormones and neurosteroid withdrawal to offer a state of chronic spontaneous seizures after a latent period.[39] The frequency and severity of spontaneous, or evoked, seizures are utilized as indices of catamenial seizure exacerbation. For a detailed review of each model, see Reddy.[34]

4.1 | Critiques and future directions

Although animal models continue to play a significant role in advancing our understanding of the molecular mechanisms of catamenial epilepsy, a valid animal model should reflect specific criteria for it to represent the human condition. It should show sufficient similarity in eliciting a catamenial epilepsy-like state and a pathophysiology that reflects the condition in women.[40] For instance, it should mirror the spontaneous recurrent seizure exacerbation (as in the third category of models) rather than acutely inducing seizures (as in the traditional models of the first and second categories).[40] The absence of spontaneous recurrent seizures in the traditional models raises concern over whether these models represent epileptogenesis or an acute increase in seizure susceptibility.[41] The neurosteroid withdrawal model in epileptic animals provides some advantages over the traditional models, yet it still does not mirror the neuroendocrine conditions of the human state, because the neurosteroid withdrawal is externally and abruptly induced.

Many of the candidate mechanisms covered in Part 1 of this two-part review rely on time-specific dynamics.[42]

Examples include the estradiol:progesterone ratio changes as well as prolonged exposure to ALLO (and thus the induction of $GABA_A$ receptor-mediated tolerance and withdrawal mechanisms) in the mid-luteal phase. One of the biggest challenges in overcoming this is that although the above hormonal conditions can be introduced in animal models and do shift seizure likelihood,[32] they do not explain why not all females with epilepsy are affected. There may be an adaptation or plasticity mechanism that is unknown, and they do not provide precise insight for treatment targets.

Catamenial epilepsy in humans is a multifaceted condition that encompasses a myriad of potential causes and seizure phenotypes.[32] Thus, it is doubtful that a single animal model could encapsulate the full spectrum of seizure phenotypes or the potential underlying molecular mechanisms. Reddy[32] suggested that this might be overcome by investigating a battery of animal models; however, the challenge of validating each of these models still holds. Thus, developing methods to investigate the condition directly in humans is warranted for a better understanding of the underlying mechanism of catamenial epilepsy.

More studies in humans that are focused on determining the mechanism of catamenial epilepsy are needed. These would ideally be focused on why some but not all females are affected and so may be best carried out in females who have the most exacerbations (e.g., fivefold or higher, or exclusively catamenial seizures). This information could be used to inform the development of animal models for preclinical or invasive investigations.

There are, however, numerous challenges with studying humans. Although we make recommendations for classifying catamenial epilepsy using seizure and menstrual cycle diaries in this review, it remains a limitation in research that the only available evidence for the existence of catamenial epilepsy in humans is seizure count, which relies entirely on patients' self-report of seizure occurrence. This not only raises concerns about the subjectivity of self-reports and issues with adherence to diaries but also the validity of seizure count as a diagnostic measure in the context of catamenial epilepsy. Whereas two studies have confirmed the reliability of patients' seizure memory,[43,44] others have demonstrated that patients have failed to document half of their seizures.[12-15] Underreporting of seizures was found to be an issue irrespective of whether patients themselves or their caregivers were maintaining the diary.[16] Even tonic–clonic seizures were found to be underreported in a study comparing a bedside paper seizure diary to seizure frequency detected by an accelerometer watch.[17]

Strategies that have been reported to improve compliance with seizure diaries include the use of regular reminders[43,45,46] and training patients on how to use the diaries.[47] However, failure to document seizure occurrence by patients could be related to impaired seizure awareness,[48,49] seizure occurrence during sleep,[48,50] or having asymptomatic seizures, all of which cannot be avoided via reminders or training. Another issue that was noticed during our screening of patients was a failure to recognize focal aware seizures due to a lack of knowledge about the manifestations of seizures themselves. These inaccuracies could obscure seizure cyclicity in self-reported diaries. It has been argued that because cycles are repeating patterns, periodic rhythms in seizure occurrence can still be found within noisy data if the duration of the record is sufficient.[2] However, self-reports are subject to recall and reporting biases, which could also be cyclical.[3]

Thus, these limitations clearly highlight the need for an objective biomarker for catamenial epilepsy in humans. What this biomarker will be is unclear; however, with future research, biomarkers may be found in home or long-term electroencephalographic (EEG) recording technology, or blood sample analysis beyond hormone concentrations.

There are promising developments in the field of ultra-long-term EEG monitoring using subcutaneous EEG. This may be particularly useful for patients with impaired awareness seizures.[51,52] The advancements in devices for seizure detection also hold promise,[53] although currently commercially available devices continue to only be useful in tonic–clonic seizures,[54] and all noninvasive devices rely on some motor component to the seizure. Current devices are most accurate when patient-specific algorithms are used.[54] In clinical research on catamenial epilepsy, collaborations with computational engineers and related fields in medical and wearable devices may lead to both improved objective seizure tracking and the ability to include a more diverse sample.

Maguire and Nevitt[55] recently identified a paucity of high-quality clinical trials, meaning there is no strong evidence base for potential treatments for catamenial epilepsy. Current practices that have been studied include clobazam (which may be tapered in the luteal phase), acetazolamide, progesterone (may also be tapered), norethisterone, and complete suppression of the menstrual cycle (e.g., gonadotropin-releasing hormone [GnRH] analogues or agonists, medroxyprogesterone acetate [MPA], sustained oral contraceptive use).[55] Treatments like GnRH antagonists, MPA, and other agents that suppress the menstrual cycle are also incompatible with conceiving or the desire for a natural menstrual cycle, adding to the treatment burden of epilepsy for female patients.

One of the key hormones discussed with regard to catamenial epilepsy is ALLO. Promising progress in

the field of central nervous system drug development, particularly for psychiatric indications, includes the approval of drugs such as ALLO (Zulresso/brexanolone[56]) and other compounds that interact with ALLO's effects on the brain (e.g., sepranolone[57]). This approach of ALLO modulation holds promise for catamenial epilepsy. However, only high-quality, well-designed, rigorous clinical trials with humans that overcome the many challenges discussed in this review can determine its potential efficacy.

5 | GENERAL CONCLUSIONS

In this review, we provide an overview of the literature on incidence and current classification of catamenial epilepsy. Recommendations for classification of catamenial epilepsy using case examples are described with the intention that these be implemented in future studies and may be easily adapted to become clinically useful, especially if they are to be implemented in an app or other digital framework alongside seizure and menstrual cycle diaries. However, future trials would benefit from the advancement of objective seizure detection devices.

Further research in humans affected by catamenial epilepsy is needed to complement a current dominance of animal models. The pathophysiology appears to be dependent on receptor and hormone sensitivity, which may have key temporal dynamics or be nonequivalent across species. Improved understanding of the specific mechanism underlying catamenial seizure exacerbation from human studies could update animal models. To permit more informative, mechanism-focused research in humans, the need for both consistent classification of catamenial epilepsy and an objective biomarker is highlighted.

AUTHOR CONTRIBUTIONS

Malak Alshakhouri: Conceptualization (supporting); writing–original draft (lead); writing–review & editing (equal). **Cynthia Sharpe**: Writing–review & editing (supporting). **Peter Bergin:** Writing–review & editing (supporting). **Rachael L. Sumner:** Conceptualization (lead); writing–original draft (supporting); writing–review & editing (equal); funding acquisition.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

PATIENT CONSENT STATEMENT

All participants provided written, informed consent for the use of their data for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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