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Review

Progesterone and its derivatives for the treatment of catamenial epilepsy: A systematic review

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ABSTRACT

Objective: Catamenial epilepsy (CE) is defined as an increase in seizure frequency during specific phases of the menstrual cycle in women with epilepsy. The treatment usually includes a combination of non-hormonal and hormonal therapies. This systematic review summarizes the available data on the efficacy of progesterone and its derivates to treat CE.

Methods: We performed a systematic search of the literature to identify studies reporting data on the use of progesterone and its derivatives (any type and dose) for the treatment of CE. The main outcome included the efficacy of progesterone and its derivatives on seizure frequency.

Results: Nineteen articles (457 patients) were included; four were randomized controlled trials (two comparing progesterone vs placebo and two comparing norethisterone vs placebo). Progesterone was generally administered during the luteal phase (from day 15 to 25) or during perimenstrual exacerbations (from day 23 to 25), with an average dose of 10–30 mg/day to a maximum of 300 mg/day. The therapy, usually well tolerated, was ineffective in the randomized controlled trials; conversely, it was associated with an overall reduction in seizure frequency in case reports and uncontrolled studies.

Conclusions: Although data from uncontrolled studies suggest that hormone therapy with progesterone may be useful in the treatment of CE, its efficacy has not been demonstrated in controlled trials. The possible antiseizure effect of progesterone could be mediated by its active metabolite allopregnanolone, making the plasmatic measurement of these hormones mandatory to evaluate efficacy. Further randomized controlled trials should investigate the efficacy of progesterone and its derivatives, addressing these pharmacological issues.

1. Introduction

Catamenial Epilepsy (CE) is defined as an increase in seizure frequency during specific phases of the menstrual cycle in women with pre-existing epilepsy [1]. The prevalence of catamenial epilepsy depends on the definition adopted by investigators. According to some authors, it could affect one-third to one-half of women with epilepsy (WWE) [1]. Obtaining precise epidemiological data on its incidence would be invaluable to understand the relevance of this condition (avoiding under- or over-estimates) and inform clinical practice.

Although the exact hormonal mechanisms underlying CE are not completely understood, sex hormones have neuroactive effects. The proconvulsant effects of estradiol [2] and anticonvulsant effects of progesterone [3] could explain different patterns of seizure distribution

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during the menstrual cycle of WWE.

During the mid-luteal phase, when progesterone levels increase, WWE may experience a seizure reduction [4,5]. In ovulatory cycles, seizures tend to cluster during the perimenstrual phase, due to the so-called "progesterone withdrawal" [6], as well as during the mid-cycle, following the increase in estradiol levels and, consequently, in the estradiol/progesterone ratio [7]. In anovulatory cycles, which are particularly common in WWE [4,5,8–11], seizures increase during the second half of the cycle (luteal phase), possibly because of low progesterone levels[12,13].

Based on these observations, CE can be classified into three distinct patterns: perimenstrual (C1) and periovulatory (C2) exacerbations of epileptic seizures during normal cycles, and increased seizure frequency in the entire second half of the cycle (C3) during inadequate luteal phase cycles [14].

There is still some controversy regarding the existence and prevalence of catamenial epilepsy. Some authors report a high prevalence of 60–70% of women with epilepsy [15]. However, all of them defined catamenial epilepsy in terms of just more perimenstrual seizures as compared to other phases of the cycle, without taking into account the definition and classification described above. Herzog et al., on the other hand, report a prevalence of catamenial epilepsy by pattern as follows: C1 pattern seizure exacerbation occurred in 39.8%, C2 pattern in 33.9%, and C3 pattern, in 47.1% [15].

Current treatments of CE include non-hormonal therapies with acetazolamide or clobazam and hormonal therapy with cyclic progesterone[16]. No clear guidance is available in the literature about the dose, time of administration, and duration of these therapies. Furthermore, data on the antiseizure efficacy of progesterone are conflicting. Treatment is generally administered during the C3-luteal phase (from day 15 to 25) or during the C1-perimenstrual phase (from day 23 to 25) [17], but without agreement on the most appropriate dosage, that can vary from an average oral dose of 10–30 mg/day [18] to a maximum of 300 mg/day [19].

Data on efficacy are also conflicting: even though single case reports and small observational studies reported an overall reduction of seizure frequency [17,19–22], this was not confirmed in larger randomized controlled trials [23,24].

We, therefore, conducted this systematic review to clarify the efficacy of progesterone and its derivatives for the treatment of CE. For a better understanding of the main topic dealt with in this review, we also provided an introductory brief narrative overview on experimental models of CE and progesterone fluctuations during the cycle in WWE.

1.1. Experimental models of catamenial epilepsy

Animal models of catamenial epilepsy differ from the traditional induction models, which utilize pilocarpine, chronic kainite acid, or hippocampal kindling to create an extreme damage and remodeling response in the brain [25,26]. Unlike these models, CE is related more to changes in hormonal concentrations rather than to structural brain damage. The best animal model to study CE consists therefore of the exogenous (i.e., through hormonal injection) or endogenous (i.e., through gonadotropin injection) induction of prolonged and elevated levels of progesterone and estrogens in rodents, followed by a sudden fall in their concentrations through finasteride injection, that imitates the sexual hormones fluctuations during menstrual cycle [27].

Animal studies showed that neurosteroids influence neuronal activity through different pathways. Firstly, progesterone and its metabolites seem to modulate neuronal excitability leading both to cortical excitation and cortical inhibition. The excitatory activity is mediated by the interaction with the progesterone receptors, which potentiate the glutamatergic activity [28]; conversely, the inhibitory activity is mediated by the stimulation of the GABA-A receptors via its active metabolites 5α, 3α-tetrahydro-progesterone (allopregnanolone, AP) [29]. Furthermore, neurosteroids interact with synaptic and extrasynaptic GABA-A receptors in a concentration-dependent relation: higher concentrations of AP directly activate GABA receptors, whereas low concentrations potentiate GABA-gated currents. Interestingly, unlike benzodiazepines, chronic exposure to neurosteroids does not lead to tolerance [30,31].

Neurosteroids can also mediate an enduring cyclical neuronal plasticity in response to their natural fluctuation. During the perimenstrual phase, there occurs an up-regulation of extrasynaptic δ-GABA-A receptors, which mediate tonic inhibition; however, this is not sufficient to counterbalance the increased seizure susceptibility triggered by the progesterone reduction in the luteal phase [32].

In conclusion, progesterone seems to have a bimodal action on cortical excitability, causing excitation when acting on its receptor, and inhibition mediated by its active metabolites (AP) through GABA-A receptors. Overall, progesterone appears to have anti-seizure effects, and seizure susceptibility is inversely correlated to its serum levels. These findings provide the rationale for investigating the efficacy of progesterone, and especially AP, for the treatment of CE.

1.2. Progesterone levels in different stages of the menstrual cycle in women with epilepsy

In addition to the preclinical studies mentioned above, blood levels of progesterone have been measured in different stages of the menstrual cycle to assess their influence on the seizure frequency of WWE. These results, however, are often conflicting.

One study found that progesterone levels were lower in WWE compared to healthy controls, while other studies found low levels of progesterone and estradiol in both WWE and controls [13,33,11], and in a few studies the difference was not significant [34]. Although these results may seem to contradict the previous hypothesis, it is worth noticing that plasma levels do not always reflect the changes occurring in the brain. Furthermore, variations can occur only in the seizure exacerbation phase, and not in the interictal phase, therefore the timing of the sampling plays a crucial role [35,36].

The influence of progesterone on seizure frequency is particularly relevant for focal seizures evolving to bilateral tonic-clonic seizures. A higher daily average seizure frequency of 29.5% in this seizure type was found in women with an anovulatory menstrual cycle compared to women with an ovulatory cycle; this finding was correlated with differences in estradiol/progesterone (E/P) ratio [10]. During high progesterone phases in ovulatory menstrual cycles a decrease in seizure frequency occurs, whereas during high estradiol phases in anovulatory cycles, seizure frequency increases [4,5].

Considering that, as mentioned above, the antiseizure effect may be determined by the metabolite allopregnanolone rather than by progesterone itself, Herzog et al. evaluated the correlation between percentage changes in allopregnanolone levels and seizure frequency from baseline in progesterone-treated WWE. The authors found a significant reduction of seizure frequency in the subgroup of subjects who had a 3-fold or greater increase in average daily seizure frequency during the perimenstrual phase compared to the mid-follicular and mid-luteal phases [37].

In addition to these clinical observations, progesterone exerts neurophysiological effects. During the menstruation phase, there occurs an increase in epileptic discharges [38,39], whereas the infusion of progesterone reaching luteal phase plasma levels during the first week of the menstrual cycle can reduce epileptic focal discharges in WWE [40]. Furthermore, the intravenous infusion of estrogen is associated with rapid interictal epileptiform activity in WWE, while estrogen given premenstrually can cause seizures [2].

Overall, these data suggest that catamenial epilepsy can be interpreted as a "neurosteroid withdrawal" disorder [6].

2. Material and methods

Results of this systematic review were reported according to the

recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [41] extension statement for network meta-analyses [42] (Appendix). The review protocol was not previously registered.

We systematically searched the following electronic databases and data sources: MEDLINE (accessed through PubMed), EMBASE, and Google Scholar. The following search strategy was used: ('progesterone'/exp OR progesterone) AND ('epilepsy'/exp OR epilepsy OR 'seizure, epilepsy and convulsion'/exp OR 'seizure, epilepsy and convulsion' OR 'seizure'/exp OR seizure). The searches were conducted on November 8, 2022.

We included any clinical study type providing data on the efficacy of progesterone and its derivatives (any type and dose) on the seizure frequency in CE. We excluded preclinical studies conducted in vivo or animal models, and articles not providing data on the efficacy of progesterone and its derivatives. We evaluated efficacy as the percentage of seizure frequency reduction according to specific catamenial patterns. No language restrictions were adopted.

Nine reviewers working in pairs (B.N., J.L., G.E., F.R., F.D., M.T., S. T., and F.N.) independently screened the retrieved articles for possible inclusion. Disagreements were discussed collegially and resolved through discussion. Data were extracted on a pre-specified digital spreadsheet.

The quality of non-randomized trials was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS). This score ranges from 0 to 9, with studies getting scores ≥ 5 being considered as having good quality (Fig. 2) [43]. The quality of randomized controlled trials (RCTs) was evaluated with the Cochrane risk of bias tool for randomized trials (Fig. 3) [44].

The following patient data were independently extracted: age; comorbidity; seizure semiology, frequency, and etiology; type of epilepsy syndrome; history of status epilepticus; pattern of CE (C1, C2 or C3); EEG features; ASM administered (number, type and dosage, treatment duration, side effects); hormonal therapy (type, formulation, dosage, days of administration, treatment duration, side effects); serum levels of progesterone and its metabolites (pre- and post-treatment); co-treatments; follow-up duration.

Results were summarized qualitatively due to the high clinical and methodological heterogeneity across included studies. Detailed informations of characteristics of RCTs and other studies are reported in the supplementary material.

3. Results

The literature search reported above yielded results 1995 (MEDLINE: 548; EMBASE: 1427; Cochrane Library: 1; other sources: 19). After excluding 471 duplicates and reading title and abstracts, 28 articles were initially considered. After reading the full-text, 9 articles were eventually excluded and 19 articles included (Fig. 1).

3.1. Included studies

Nineteen articles were included: four RCTs (two comparing progesterone versus placebo: Herzog 2012, Najafi 2013; two comparing norethisterone versus placebo: Dana-Haeri 1983, Cleland 1995) [23,24,45,46], five non-randomized cross-over clinical trials (Mattson 1984, Herzog 1986, Herzog 1995, Herzog 1999, Motta 2013) [17,22,47–49], one prospective cohort study (Backstrom 1984) [18], three case series

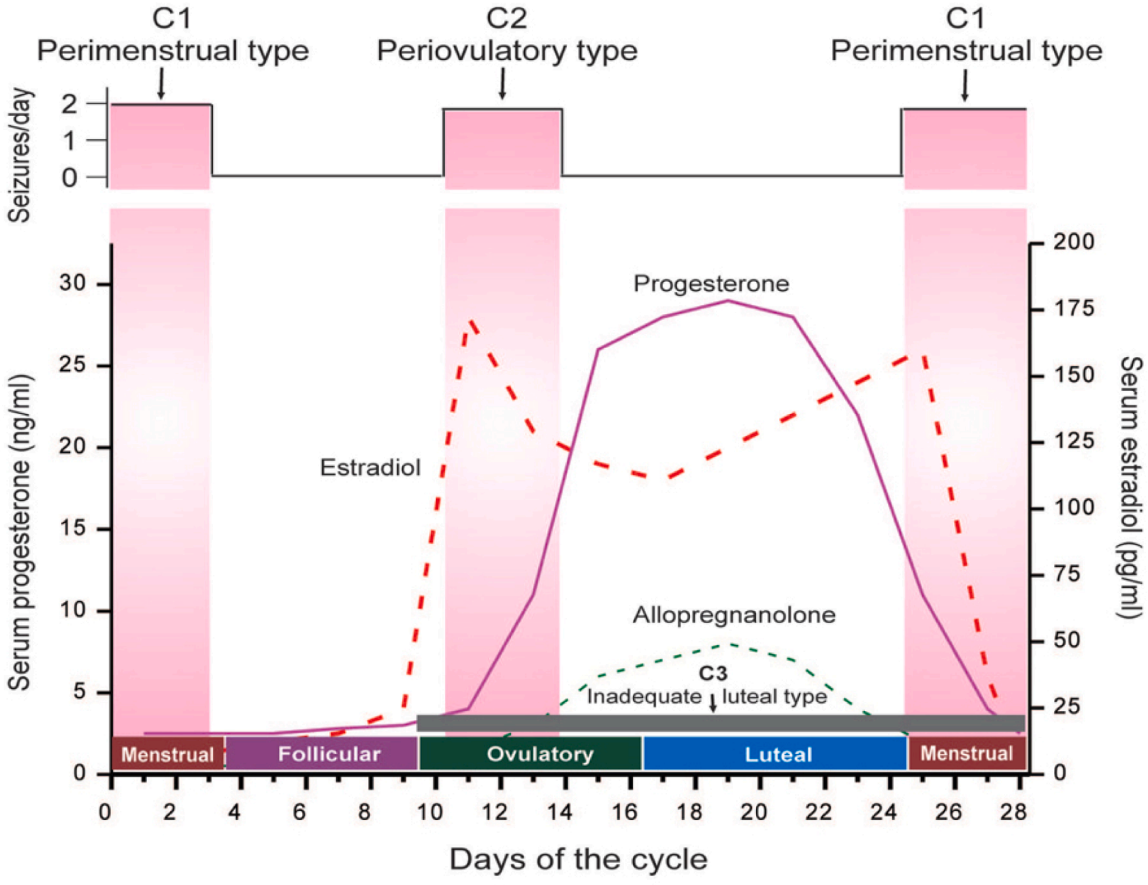

Fig. 1. Graphic representation of hormonal changes during cycle and the three different pattern of catamenial epilepsy. From: Reddy DS. Catamenial Epilepsy: Discovery of an Extrasynaptic Molecular Mechanism for Targeted Therapy. Front Cell Neurosci. 2016 Apr 22;10:101 [reference 27]. Copyright © 2016 Reddy, reproduction authorized under the terms of the Creative Commons Attribution License (CC BY).

(Macias 2009, Lotte 2018, Kim 2020) [19,21,50], and six case reports (Zimmerman 1973, Hall 1977, Grunewald 1992, Herzog 2003, Kandeepan 2016, Feyissa 2019) [20,51–55].A total of 457 women (age range: 9–40 years) were included. According to Newcastle-Ottawa Quality Assessment Scale (NOS) the quality of the studies was judged as low (14 articles) or adequate (1 article) (Fig. 2).

With regards to the appraisal of the methodological quality of included RCTs, the overall risk of bias was moderate in 3 RCTs (Najafi et al., 2013; Herzog, 2012; Dana-Haeri, 1983) [24,23,45], and high in one RCT (Cleland, 1995) (Fig. 3) [46]. Detailed results of critical appraisal and evaluation of the risk of bias for included RCTs are reported in the supplementary material (Fig. 4).

4. Randomized controlled trials comparing progesterone to placebo

Two placebo-controlled, double-blind, parallel trials compared progesterone to placebo. One was a multicenter study [23] and the other was conducted in a single center [24].

Herzog et al. [23] included women with EEG-confirmed focal onset drug-resistant epilepsy, with a seizure frequency of two or more seizures per month during the 3 months before enrollment. In a 3-month baseline, women recorded data on seizures and menses, and they were classified into catamenial or non-catamenial stratum, using pre-specified criteria [Herzog et al. criteria]. Catamenial strata included the three types of seizure pattern: C1: perimenstrual, C2: periovulatory, or C3: entire luteal phase. Catamenial strata (130) and non-catamenial strata (164) were separately randomized 2:1 to progesterone or placebo. Progesterone treatment consisted of progesterone 200 mg (Lozenges), administered 3 times daily on days 14 –28 of treatment cycles for 3 months. 85 catamenial patients were treated with progesterone and 45 with placebo: no significant difference was found in the primary outcome of ≥50% reduction in all seizures during treatment as compared to the baseline (progesterone: 18/79, 22.8% vs placebo: 9/45, 20.0%; p-value: 0.718). Adverse effects were reported in 37 of 85 women (43.5%) and included: diarrhea, dyspepsia, nausea, vomiting, fatigue, nasopharyngitis, dizziness, headache, and depression. The authors also reported 22 serious adverse events among the whole population (462 women). Of the 9 adverse events during the treatment phase, 6 occurred with progesterone and 3 with placebo. The most common (12/22) was hospitalization for seizures. One death occurred on progesterone, which was attributed to sudden unexplained death in epilepsy.

A post hoc analysis of the same RCT showed that the pattern of perimenstrual seizure exacerbation (C1) was a significant predictor of ≥50% reduction in all seizures in patients receiving progesterone vs patients receiving placebo. Among women with the C1 pattern, responders increased from 21% to 57% with progesterone vs 19% to 20% with placebo.

A second RCT [24] included women with focal or generalized seizures and catamenial pattern, defined as seizures exacerbations during premenstrual (C1: day −3 to day +2) or during the entire luteal phase (C3: day 2 to day 10), and with a low progesterone level (< 5 mg/mL) in the mid-luteal phase for luteal exacerbations (CIT). Following a 3-month baseline period, women were randomized to either placebo or progesterone. Progesterone treatment consisted of 40 mg bid of progesterone (Mejestrol) taken for 11 days, in the second half of the cycle from the 15th to the 25th day, and subsequently discontinued. The duration of

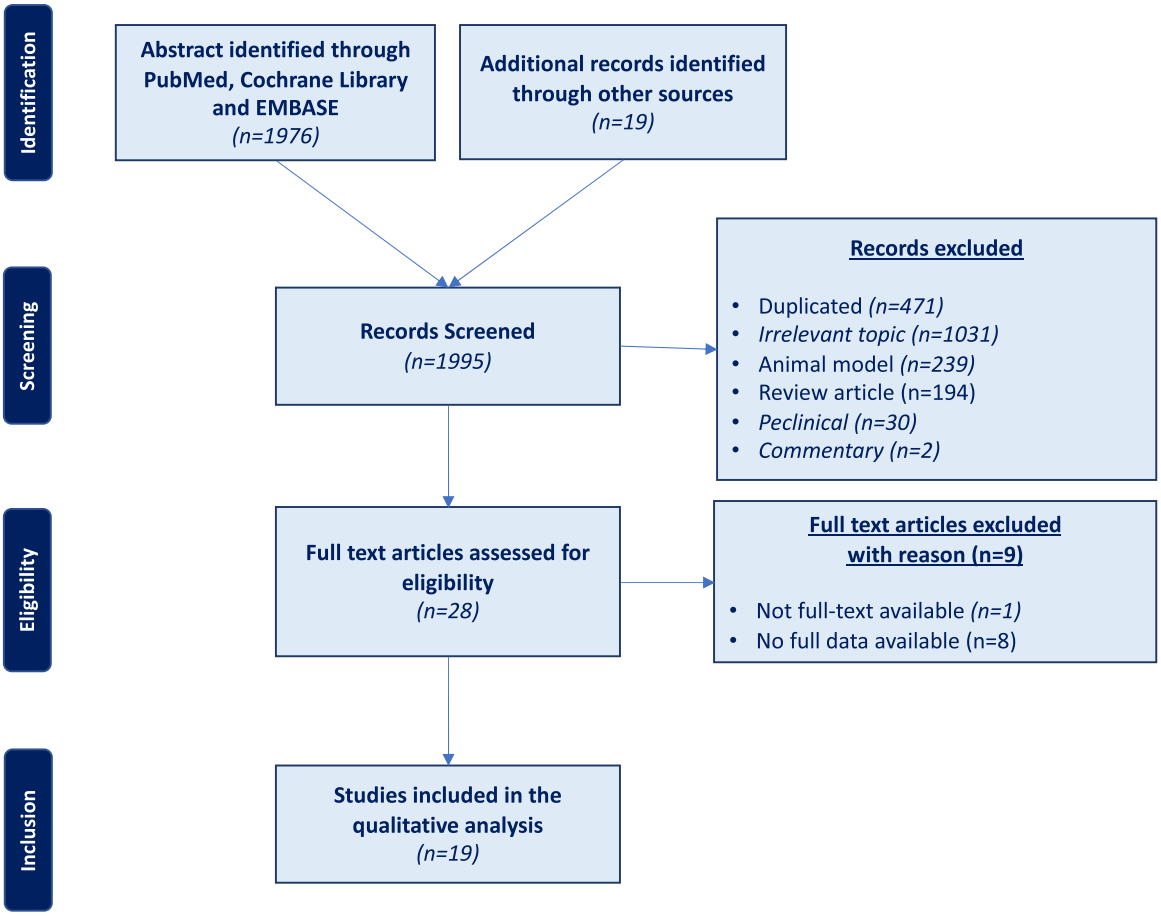

Fig. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram describing the search from literature; 1871 records were screened, from which 28 articles were selected.

Authors	Year	Risk of bias N	1) Represent	2) Selection c	3) Ascertainr	4) Demonstr	5) comparab	6) Assessme	7) Was follov	8) Adequacy	score totale (<5 low quality, >7 high quality)
Kandeepan J, Shaaban J	2016		0	1	0	0	0	0	0	0	1
K. A. Rodriguez Macias	2009.		1	0	1	1	0	0	1	1	5
Torbjorn Backstrom et al.	1984		1	0	1	1	0	1	0	0	4
R.A. Grunewald et al.	1992		1	0	1	1	0	1	0	0	4
Susan M. Hall	1977		1	0	1	1	0	0	0	0	3
Jon Soo Kim et al.	2020		1	0	1	1	0	0	0	0	3
Anteneh Feyissa et al.	2019		1	0	1	1	0	0	1	1	5
Andrew W. Zimmerman et al.	1973		1	0	1	1	0	1	0	0	4
Andrew G. Herzog	2003		1	0	0	0	0	1	0	0	2
Jan Lotte,Stefan Grothe, Gerhard Josef Kluger	2018		1	0	1	1	0	0	0	0	3
Andrew G. Herzog	1995		1	1	1	1	0	1	0	1	6
Ewa Motta et al.	2013		1	1	0	1	1	0	0	0	4
Richard H. Mattson, Joyce A. Cramer, Burton V	1984		1	0	1	1	0	0	1	1	5
Andrew G. Herzog	1986		1	0	1	1	0	0	1	1	5
Andrew G. Herzog	1999		1	0	1		0	0	1	1	4

Fig. 3. Quality assessment of non-randomized studies using the Newcastle-Ottawa Quality Assessment Scale (NOS).

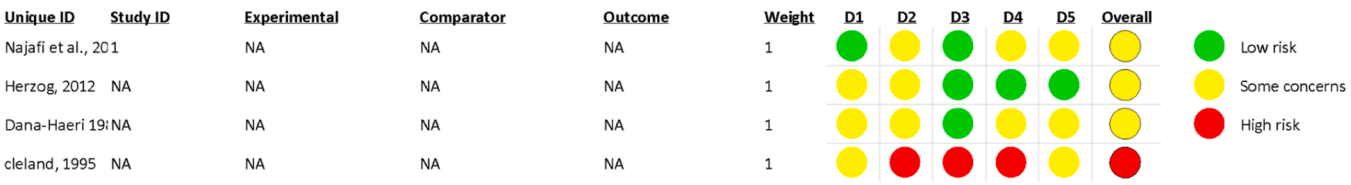

Fig. 4. Quality assessment of randomized controlled trials (RCTs) with the Cochrane risk of bias tool for randomized trials.

treatment was 3 months. The authors enrolled 38 women (mean age 30.5 years): they were randomly allocated to progesterone or placebo (19 patients in each group). There was no statistically significant difference in age, body mass index, epilepsy duration, and progesterone levels between the two groups (inter-group comparison). In each group (intra-group comparison), the frequency of seizures evaluated at 3 months decreased compared to the 3 months of baseline assessment, and the reduction was larger in WWE allocated to progesterone (p-value = 0.024). Two women withdrew due to progesterone side effects (severe headache, nausea, and vomiting). No further information on adverse events was reported.

5. Randomized cross-over trials comparing norethisterone to placebo

Two small single-center, double-blind, randomized cross-over trials compared norethisterone with placebo.

Dana-Heari et al. [45], enrolled women aged between 20–30 years with an increased seizure frequency before (luteal phase) or during menstruation in at least 5 of 12 menstrual cycles. Seizure semiology was tonic-clonic seizures and complex or simple partial (i.e., focal impaired awareness or focal without impaired awareness) seizures. Women were randomly assigned to placebo, norethisterone 5 mg three times daily, or norethisterone 350 μg three times daily. Every four menstrual cycles the patients were shifted from one treatment regime to the other or placebo, and the order of the three treatments was random. At the end of the 12 cycles, each woman was observed for 1 to 2 months without taking any hormonal treatment. The study enrolled nine patients, none of which showed a significant decrease in seizure frequency, either during the low or during the high norethisterone treatment. No adverse effect was reported.

Cleland et al. [46], 1995 conducted a trial on documented catamenial exacerbation of epilepsy. No further information regarding inclusion/exclusion criteria or the type of seizures was reported. The authors enrolled 15 patients, randomized to norethisterone (0.35 mg daily) or placebo for 6 months, followed by a 2-month wash-out period, and then by 6 months of the other treatment. The author reported no statistically significant differences between the treatment groups; however, no further details were provided to support this conclusion. Eight of the 15 patients reported adverse events, but only four of these were related to the trial medication. Side effects included irregularities in the menstrual cycle, facial rash, headaches, mild swelling of hands and feet, and bloated feeling.

6. Observational studies

The remaining observational studies included data on 120 patients (age range: 9–40 years). The results of these studies are reported in the following sections.

6.1. Demographics, epilepsy features, and antiseizure medication

In most patients (71/120, 59.16%), seizures were described as complex partial (i.e., focal impaired awareness), and generalized (Backstrom 1984, Herzog 1986, Herzog 1995, Herzog 1999, Herzog 2003, Macias 2009; 10/36 in Motta 2013) [18,19,22,48,49,54], and as generalized seizures in 24 (20%) patients (Zimmerman 1973, Hall 1977, Grunewald 1992, Lotte 2018, Kim 2020; 16/36 in Motta 2013; 1/14 in Mattson 1984) [21,22,47,50–53]. Focal seizures were reported in 22 patients (18.33%) (Mattson 1984, Motta 2013) [22,47], 8 of which with impaired awareness (Motta 2013) [22], and 3 with evolution to bilateral tonic-clonic seizures (Kandeepan 2016, Feyssa 2019, in Motta 2013) [20,22,55].

Etiology was reported in 18 patients: 13 had structural epilepsy (Motta's clinical trial, Backstrom's cohort study) [18,22], one had post-inflammatory (Feyissa) [55], one had post-infective (Backstrom's cohort study) [18], one had post-anoxic encephalopathy (Herzog 2003) [54], and two had genetic epilepsy (Lotte 2018) [50].

Seizures frequency was yearly in 7 patients (7/120, 5.83%) (Macias 2009, Kim 2020) [19,21], weekly/monthly in 30 patients (25%) (Hall 1977, Backstrom 1984, Mattson 1984, Herzog 1986) [18,47,48,52], and daily during the menses in 41 patients (34.16%) (Zimmerman 1973, Grunewald 1992, Motta 2013, Kandeepan 2016, Lotte 2018) [22,20,50,51,53].

The use of an antiseizure medication (ASM) was reported in 65 (54.16%) patients (Zimmerman 1973, Hall 1977, Backstrom 1984, Herzog 1986, Grunewald 1992, Herzog 2003, Macias 2009, Motta 2013, Kandeepan 2016, Lotte 2018, Kim 2020) [19–22,50–54]. The most frequent monotherapy treatment was carbamazepine (22/120 patients, 18.33%) (Backstrom 1984, Herzog 1986, Macias 2009, Motta 2013) [18,19,22,48], followed by valproic acid (14/120, 11.66%) (Macias 2009, Motta 2013) [19,22], diphenylhydantoin (6/120, 5%) (Herzog 1986,

Backstrom 1984) [18,48], and phenytoin (4/120, 3.33%) (Motta 2013) [22].The other ASM monotherapies were primidone (3/120, 2.5%) (Backstrom 1984) [18], clonazepam (1/120, 0.83%) (Backstrom 1984) [18], and phenobarbital (1/120, 0.83%) (Hall 1977) [52].

6.2. Pattern of catamenial seizures

The pattern of seizure exacerbation was reported in 88 (73.3%) women. Fifty-one patients (51/120, 42.5%) had a C3 pattern (Herzog 1995, Herzog 2003, Motta 2013) [17,22,54], while 25 women (25/120, 20.8%) had a C1 pattern (Zimmerman 1973, Hall 1977, Backstrom 1984, Herzog 1995, Macias 2009, Kim 2020) [17–19,21,51,52]. Both C1 and C2 patterns were described in one case report (Kandeepan 2016) [20] and both C1 and C3 patterns in another one (Grunewald 1992) [53]

6.3. Progesterone formulation and administration

Oral progesterone 200 mg three times daily or 300 mg once daily was used in 41 (34.16%) (Herzog 1995, Herzog 1999, Herzog 2003) [17,49,54], and 5 (4.16%) women (Macias 2009) [19], respectively. Oral medroxyprogesterone acetate was given 5 mg twice a day in 36 (30%) women (Motta 2013) [22], and 10 mg once a day (Kim 2020) [21] in 2 (1.6%). A woman received oral medroxyprogesterone acetate from 10 to 50 mg once a day and then switched to a depot intramuscular medroxyprogesterone acetate (250, 250, and 150 mg) injections every 2 weeks (Zimmerman 1973) [51]. A similar approach was used in 15 (12.5%) patients: they were first given 10 mg oral medroxyprogesterone acetate two to four times daily, and then depot intramuscular medroxyprogesterone acetate 120–150 mg at 6–12 weeks intervals, depending on the time of breakthrough bleeding (Mattson 1984) [47]. Oral norgestrel 0.5/0.35 mg daily, intramuscular methylprogesterone 150 mg a week, and neolat/fortilat 10 mg/day followed by either oral or injection of intramuscular progesterone (Lutorn 50 mg) were given in one patient each (Hall 1977, Kandeepan 2016, Grunewald 1992) [20,52,53]. A combination treatment of ethinylestradiol 0.03 mg/dienogest 2 mg in one case and ethinylestradiol 30 μg/ levonorgestrel 150 μg in another one was also reported (Lotte 2018) [50]. Other routes of administration were intravenous progesterone 10 - 30 mg (Backstrom 1984) [18], and vaginally suppositories of progesterone 50 - 400 mg twice daily (Herzog 1986) [48].

Six studies (84 patients, 70%) further clarified when progesterone was given according to the phase of the menstrual cycle (Macias 2009, Herzog 1995, Herzog 1999, Motta 2013, Kim 2020, Herzog 2003) [17,19,22,21,49,54]. In 40 women (33.3%), the days of administration varied accordingly to the catamenial pattern: from the 23rd to the 25th day in the C1 pattern, from the 15th to 25th in the C3 pattern (Herzog 1995, Herzog 1999) [17,49]. In 44 cases (36.7%) the medication was given between the 14th-16th day and the 25th-28th day (Macias 2009, Motta 2013, Herzog 2003, Kim 2020) [19,21,22,54]. In seven women (5.8%), progesterone was given as a single dose (Backstrom 1984) [18].

The shortest period of treatment was ten weeks in one report (Kandeepan 2016) [20], while the longest was eleven years (Grunewald 1992) [53].

Progesterone serum levels were reported pre-treatment in 5 patients (4.16%) (Macias 2009) [19], post-treatment in 36 (30%) (Motta 2013) [22], and both pre- and post-treatment in 33 patients (27.5%) (Backstrom 1984, Herzog 1995, Herzog 2003) [18,17,54].

6.4. Efficacy outcomes

A significant reduction in mean seizure frequency was reported in 112 women (93.3%) during treatment with progesterone (Zimmerman 1973, Hall 1977, Mattson 1984, Herzog 1986, Herzog 1995, Herzog 1999, Herzog 2003, Macias 2009, Motta 2013, Kandeepan 2016, Lotte 2018, Feyissa 2019, Kim 2020) [17,19–22,47,48–52,54]. In four cases, no clinical effect was mentioned, but a significant reduction of electroencephalographic epileptiform discharges was observed during treatment (Backstrom 1984) [18]. An exacerbation of absences seizure was described in a woman with generalized epilepsy treated with progesterone for eleven years (Grunewald 1992) [53]. One patient achieved seizure freedom while on treatment with progesterone but had a relapse after treatment with a reductase inhibitor (finasteride) (Herzog 2003) [54].

6.5. Adverse effects

In most observational studies, no specific adverse events were reported. Mood instability was described in seven women (5.8%) (Kim 2020, Herzog 1986, Herzog 1995) [17,21,48], while sudden severe pleuritic chest pain and mild dysmenorrhea were described in one report (Hall 1977) [52]. Other reported side effects were weight gain and headache (Kim 2020), [21] spottings and delay to the resumption of a normal cycle (Mattson 1984) [47], and premature menopause (Herzog 1986) [48].

6.6. Follow-up

Data on follow-up are available only in twenty patients (16.7%), with a duration of follow-up ranging from 3 months to 3 years (Mattson's trial, Herzog 1999, Herzog 1995) [17,47,49].

7. Discussion

Our systematic search of the literature led to the inclusion of 19 studies investigating the role of progesterone and its derivatives in the treatment of women affected by CE. There is a lack of robust evidence coming from large, informative, and well-conducted RCTs. Remarkably, two RCTs did not perform a calculation of statistical power and were likely to be underpowered; therefore, the absence of a positive effect of the treatment with progesterone could represent a false-negative finding due to the low informative potential of these RCTs studies [23].

Only one comparative trial had a large sample size but failed to confirm the possible favorable effect of progesterone in the treatment of CE, showing no significant difference in the proportion of responders between progesterone and placebo in the catamenial (22.8% vs. 20%) and non-catamenial (20.2% vs. 19.2%) groups [23]. However, a post hoc analysis showed that the increased ratio of perimenstrual/baseline seizure frequency in the C1 catamenial pattern (C1 level) could predict better seizure control [23].

The paucity of trials conducted on CE contrasts with the abundance of studies on animal models showing promising results [29]. This discrepancy is likely to be related to the peculiarity of this disease. Catamenial epilepsy is characterized by seizures that occur during specific phases of the menstrual cycle (perimenstrual (C1) and periovulatory (C2) exacerbations of epileptic seizures during normal cycles, and increased seizure frequency in the entire second half of the cycle (C3) during inadequate luteal phase cycles), usually in patients with occasional seizures (often occurring monthly) [9]. This could limit the inclusion of a sufficient number of patients who requires an adequate length of follow-up to evaluate the efficacy of the tested drug. Furthermore, if one adopts the definition and classification provided by Herzog et al. [15], catamenial epilepsy is not a frequent condition, making it even more complicated for researchers to find and recruit an adequate number of participants.

The possible therapeutic effect of progesterone has been evaluated by case reports and case series [19,50,21,51,52,53,54,20,55]. Hormonal treatment included the use of progesterone, its synthetic derivatives, and complex preparations containing progesterone and estrogen components.

Most of these studies evaluated the effects of progesterone and its derivatives in patients with focal epilepsies [18,48,49,54,19,22]. Although the daily dosage of progesterone varied greatly between

studies (from 30 mg/daily to 800 mg/daily) [18,48], most of the studies showed a net reduction of the seizure frequency and sometimes seizure freedom (Logothetis, 1959, Herzog, 1986, Herzog, 1995, Rodriquez-Macias et al. 2009, Mattson et al. 1984) [2,48,17,19,47]. One study, however, did not observe any clinical response to the treatment with norethisterone, a synthetic progesterone derivate, in a cohort of women with focal or focal-to-bilateral tonic-clonic catamenial seizures (Dana-Haeri and Richens 1983) [45].

A few reports evaluated the role of progesterone in generalized epilepsies [51,52,53,50,21,22,22,47]. Three case reports reported seizure freedom achieved with treatment with progesterone up to 250 mg or with norethisterone 0.35 mg/day (Zimmerman et al., Mattson et al., Hall et al.) [51,47,52]. However, Grünewald et al. [53] reported a case of a woman with an increase in the frequency of absence seizures observed with progesterone administered because of irregular menstruation. Of note, positive results found in single case reports and case series could reflect reporting bias, requiring confirmation and replication in larger prospective studies with consecutive inclusion of patients.

Although not all studies reported information on side effects, the evidence available in the literature suggests that progesterone treatment in WWE is relatively safe, since no serious adverse effects were reported in most studies. The most frequently reported side effects included asthenia, headache, weight gain, and irregularities in menstrual cycles [21,48,17,52,47,48]. Nevertheless, in some cases intolerance to treatment led to discontinuation (Herzog, 1995) [17].

The analysis of the current literature revealed some important methodological limitations across studies, limiting the validity and generalizability of their findings. Furthermore, the daily dose of the treatment, the number of administrations per day, the duration of the treatment, and even the pharmacological formulation itself varied markedly among the different studies, making the comparison between different studies even more arduous. Given the variety of oral formulations of progesterone available in different countries, it is important to set homogenous standards for its administration. Some studies measured progesterone blood levels in the different phases of the menstrual cycle [24,19,18,54,17]. This could be a useful and viable way to account for differences between formulations. Moreover, the route of administration varied greatly among studies, with most of them using oral administration [17,49,54,19,22,21], but some using intravenous or intramuscular routes [20,18].

This can have implications on the pharmacokinetics of the drug, as well as on adherence to the treatment. Additionally, even though most studies focused on the C1 pattern [19,20,18,52,21,51,45,48], not all catamenial patterns were equally represented and investigated. Some of the included studies did not report the definition of CE that was adopted. Since different patterns could respond differently to hormonal therapy, evaluating the efficacy of progesterone and its derivatives in a population that includes the various CE patterns is, therefore, of paramount importance.

8. Conclusion

In conclusion, although preclinical data on the possible efficacy of progesterone and its derivates in the treatment of CE are encouraging, the best evidence available in the medical literature is insufficient to support their use in clinical practice. Given the difficulties in conducting randomized controlled trials, large prospective studies or international registries could systematically collect data on progesterone serum levels dosage and correlate them with clinical outcomes. Future studies using progesterone administered homogeneously and measuring progesterone blood levels are required to provide robust evidence on the role of this hormone in the treatment of CE.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2023.05.004.

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