Catamenial Epilepsy: Treatment and occurrence of seizures in different age groups of non-epileptic females due to hormonal disturbance

Asif Rasool[1], Muhammad Ali[1], Mujahid Hussain[1], Faisal Iqbal[1]

[1]Khwaja Fareed University of Engineering and Information technology, Rahim Yar Khan, Punjab, Pakistan

Abstract:

Catamenial epilepsy is menstrual seizures in an epileptic woman due to some hormonal disorders. Estrogen and progesterone are two reproductive hormones which fluctuates during menstruation and produce convulsant and anti-convulsant effects on an epileptic woman. CE has three categories according to menstrual phases: Premenstrual (C1), Pre-ovulatory (C2), and inadequate luteal phase (C3). Basically, two types of treatments are available: Hormonal treatment and medicinal treatment. Hormonal therapies include progesterone therapies and GnRH analog therapy. In medicinal treatments, there are some anti-convulsant drugs. In our research survey discussed below, some non-epileptic females also feel seizures, during their menstruation. Even they don't have any epileptic record in their medical history. The actual cause of seizures is the disturbance of hormones during menstruation. Epilepsy is a neuronal disorder so the disturbance of hormones is obvious is epileptic women and they experience the seizures. But non-epileptic women may have disturbance in their hormonal level due to some other factors like hypertension, phobias and diets. Then it will not a catamenial epilepsy, it is simply a hormonal imbalance.

Introduction:

Catamenial epilepsy (CE) is a series of frequent seizures in an epileptic woman correlate with menstrual cycle. (Nayméé J. Vélez-Ruiz, 2019). Seizures occur due to neuronal disorder activity of the brain categorized as partial and generalized seizures. There are two types of partial seizures. In simple partial seizures abnormal neuronal activity occurs only in one specific part of the cerebral hemisphere with the focal onset and there is no loss of consciousness. There is a loss of consciousness in simple complex seizures. Epilepsy with partial seizures is partial epilepsy. Catamenial epilepsy is a partial type of epilepsy. (A.G. Herzog, 2012).

The purpose of this article is to know about awareness, causes, effects and most effective treatment of Catamenial epilepsy. There are some contradictions related to menstruation linked epilepsy in Pakistan. From this research, we will come to know about the views and current knowledge of the female population about catamenial epilepsy.

Menstrual Cycle:

In menstrual cycle, variations in sex hormones impact the uterine lining and ovaries release an egg to enable reproduction (Jessica Le, 2020). Four phases of menstrual cycle: Menstrual phase (When women experiencing periods), Follicular phase 1-14 days (follicles are developing to mature the egg), Ovulatory phase (releasing of egg), and luteal phase 15-28 days (time from the egg's release to menstruation). The average menstrual cycle is 28 (24-35) days.

The hypothalamus–pituitary–gonadal (HPG) axis regulates the hormones of the menstrual cycle. Gonadotrophin Releasing Hormone GnRH released by the hypothalamus which triggers the anterior pituitary to release luteinizing hormone (LH) and follicle stimulating hormone (FSH). Ovaries of females are being induced to release estrogen and progesterone by LH and FSH. Then brain gets negative feedback from levels of these hormones causing the GnRH, LH, and FSH release to be reduced. Cycle length is normally between 24–35 days for women of reproductive age.

The luteal and follicular phase are two main phases. The follicular phase starts on the first day of menstruation and ends with ovulation, followed by the luteal phase until menstruation resumes, at which point the cycle repeats. Levels of estrogen and progesterone are low in the first week. Estrogen increases rapidly in this week; the late follicular phase and LH rises just before ovulation. Estrogen drops significantly in the luteal phase while progesterone surges to peak at day 21st of the cycle. (Jessica Le, 2020)

Patterns of Catamenial Epilepsy:

CE has three categories corresponding with these menstrual phases: Premenstrual (C1), Pre-ovulatory (C2), and an inadequate luteal phase (C3). In subtype C1, the level of estrogen is low but progesterone's level decreases rapidly. In subtype C2, the pre-ovulatory phase in 10-15 days of cycle, there is a rapid increase in estrogen level. (Samuel Frank, A Clinical Approach to Catamenial Epilepsy, 2020). In subtype C3, follicles cannot grow completely due to an inadequate secretion of follicle stimulating hormone FSH. Therefore, corpus luteum does not develop properly which leads to the low production of progesterone in luteal phase and Estrogen level remains on the peak. (Naymeé J. Vélez-Ruiz, 2019).

Pathophysiology:

Catamenial epilepsy is the foremost women's reproductive hormones are Estrogen and progesterone have neuroactive properties. They affect neuro-excitatory in an epileptic woman. Estrogen acts as a neuro-excitatory hormone and some women are very sensitive to its sudden impact. While on the other hand, progesterone contributes to neuro-inhibition. (Naymeé J. Vélez-Ruiz, 2019). Seizures actually occur in clusters with specific periodicity. In mathematical waveform analysis, partial epileptic woman experiences seizure correlate with their menstrual cycle. The term of Catamenial epilepsy applies when the frequency of seizures matches with the menstrual cycle.

Catamenial Epilepsy influenced by three factors: Neuroactive reproductive steroids, Estrogen and progesterone, Fluctuation in concentration of these reproductive steroids during menstrual cycle, A very sensitive response of certain brain substrates to these steroids. (A.G. Herzog, 2012).

Proconvulsant activity of Estrogen:

Estrogen has three categories: Estrone, Estradiol and Estriol. Estradiol and Estrone are only active in non-pregnant woman and Estriol produce in pregnant women. But concentration and biological activity of estradiol is more than these two types of estrogen (Eva Catenaccio1, 2016). Estradiol plays its role as a proconvulsant hormone in an epileptic woman. Neurons of the limbic system, Cerebral cortex and other regions which are sensitive to the seizure's exposure are targeted by estrogen. Estrogen has a complex mechanism of neuronal excitability. There are different physiological receptors (ERα & ERβ) on the cell membrane and nucleus. Estradiol effects the synaptic structure and functioning and disturbs the neuronal excitability. Estradiol has an ability to increase the neurotransmission of glutamate receptors and decreases the GABAergic inhibitory activity. G protein couple receptors for estrogen are also trigger by the estradiol. (Reddy D. S., Neurosteroids and Their Role in Sex-Specific Epilepsies, 2014). After the activation of ERβ receptors, estrogen increases the activity of GluA1 which is the subunit of AMPA receptor. The effect of Estrogen on hippocampal also minimize the releasing of GABA which is a neuroinhibitory transmitter. So, Estrogen activity increases the excitation and reduce the inhibition. (Suchitra Joshi, 2019).

Anticonvulsant activity of Progesterone:

Progesterone possesses anti-seizure effects through its metabolites most importantly Alopregnanolone (AP). It makes an inhibitory effect on the neurons of GABAergic. The level of AP depends upon the level of serum progesterone in an Epileptic woman. (Samuel Frank, A Clinical Approach to Catamenial Epilepsy, 2020). There are several targets in CNS on which progesterone acts and initiates its action. There are genomic and non-genomic receptors. Non-genomic receptors are: progesterone membrane receptor components, Membrane progesterone receptors and sigma receptors. The anticonvulsant effects of progesterone link with non-genomic receptors (Yinhao Violet Wu, 2018).

Numerous studies show that progesterone controls the production of different neurotransmitters. In several mouse studies, progesterone inserts an inhibitory effect which reduces the seizure's susceptibility. During the study of human models, injections of progesterone effectively decrease the wave spikes of seizures in 4 to 7 partially epileptic women. (Samuel Frank, A Clinical Approach to Catamenial Epilepsy, 2020).

Some other clinical Trials:

It is an estimation in recent studies that the occurrence of CE is 10% to 70% epileptic females. In random trials of The National Institute of health NIH, 130/294 (44.3%) epileptic women have CE. (Samuel Frank, A Clinical Approach to Catamenial Epilepsy, 2020). According to the study survey of The Neurological department of Jinnah postgraduate medical center, Karachi, Pakistan. 73/184 reproductive age female patients have catamenial epilepsy with is 39.7%. Seizures were being observed by using EEG. (Deepak Kumar, 2020)

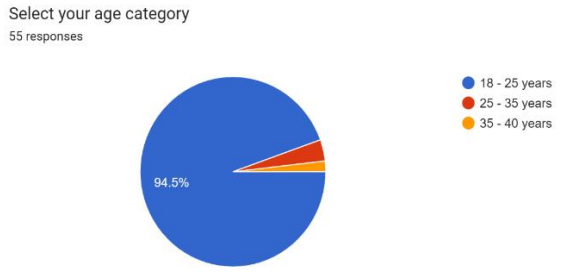
There is a division of catamenial epilepsy depends upon the pattern and reoccurring of seizures. Catamenial recurrence epilepsy common in one third drug resistance focal epileptic patients. While, catamenial status epilepticus is very rare. Only two patients had been reported in the last two years. The percentage of catamenial status epilepticus is 2/376, 0.5% in all patients under observation through invasive EEG. (Albi J. Chalissery, 2017).

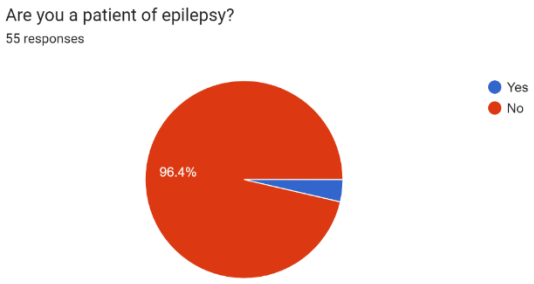
Material and Method:

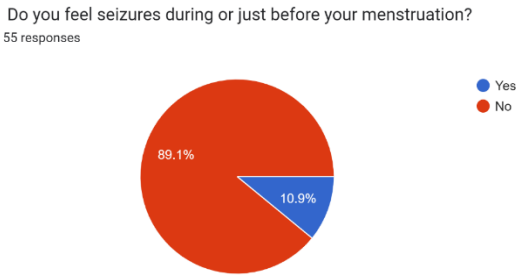
Our research group made a survey in **Khwaja Fareed University of engineering and information technology, Rahim Yar Khan, Punjab, Pakistan.** We make a google form survey and fill it from females of different age categories from 18 to 40 years. The survey contains a brief introduction about catamenial epilepsy and questions about their situations and seizures during menstruation. All females actively participate in this survey.

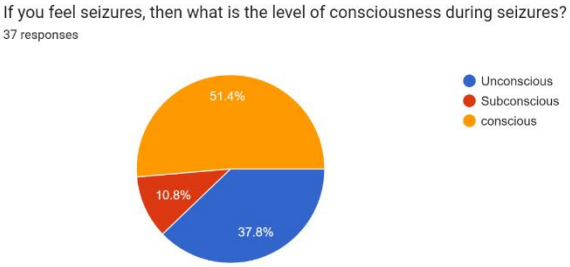
Results:

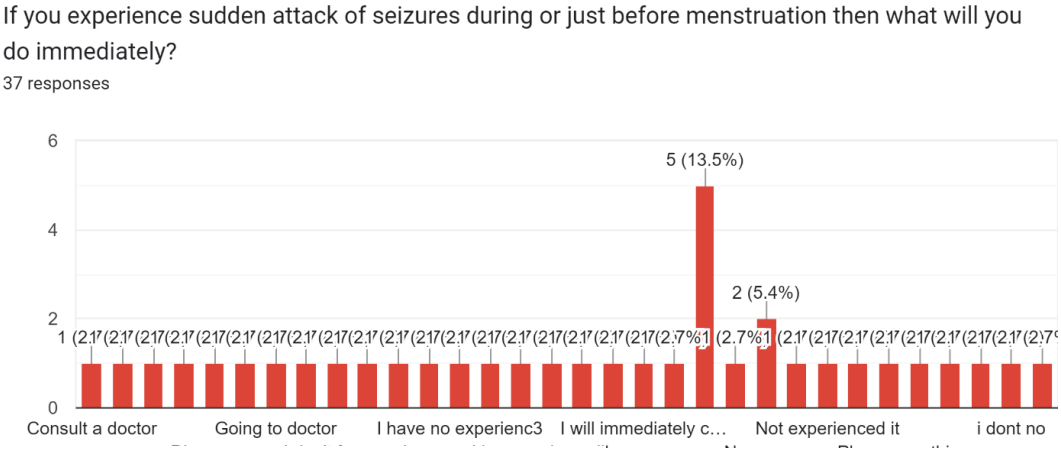
55 females participate in the survey. They answered all the questions according to their understandings. Here is the graphical representation of overall result evaluation with questions.

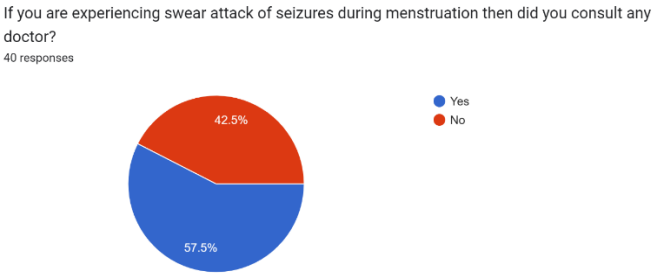


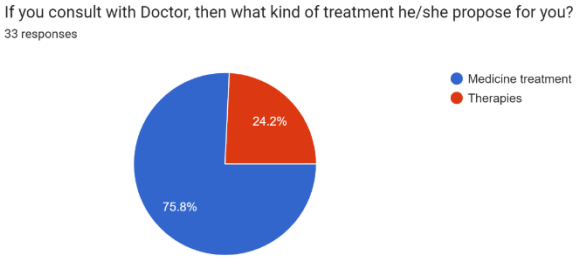


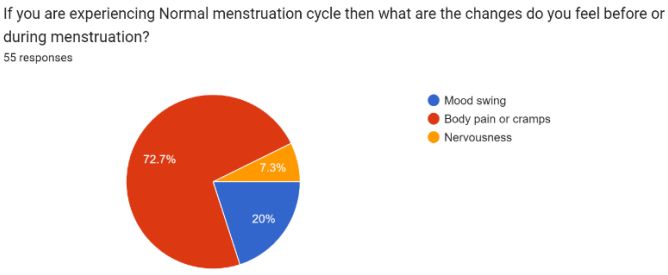


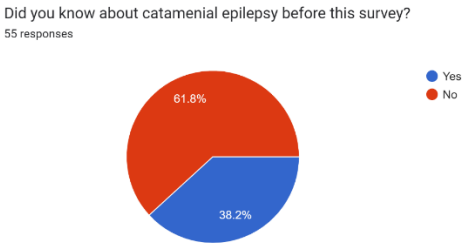












Diagnosis methodology:

There should be a proper awareness to physician or demonstrator about hormonal disturbance effects on seizures for an accurate diagnosis. The main questions should be asking from patients are: Are the seizures occurring even after the use of anti-epileptic drugs? Has the patient note down her menstrual and increasing seizure occurrence during the cycle? Are the seizures continuing in a cyclic manner? The first thing in the diagnosis of CE, advise the patient to make a record of her menstrual cycle and seizures in a diary. The physician also recommends the measurement of basal body temperature in morning orally. If there is a fluctuation in temperature about 0.7 ˚F means the starting of postovulatory phase. (Nancy Foldvary-Schaefer, 2003). There is an ovulatory dysfunction in some epileptic females. Anovulatory cycles are observed is women with focal epilepsy 14%. 39 out of 100 focal epileptic women experience anovulatory phase. A recurrence of seizures increases in anovulatory cycle. (Andrew Herzog, 2004)

Premenstrual category C1 is most common in which there is an up thrust in seizure frequency after, during or before menstruation. C1 and C2, both or only one category is present in a woman with ovulatory cycle. The diagnosis of anovulatory or ovulatory cycle makes by knowing the level of progesterone in mid of luteal phase. There is an inadequate luteal phase C3 if the level of progesterone is lower than 5ng/ml at the 20 out of 22 day of menstrual cycle. The patient will experience anovulatory cycle in C3 category. The seizures begin at puberty. Because the menstrual cycle begins after the entrance of the female in puberty. Reproductive hormones also show a peak level at that time. That's why during the fluctuation of hormonal concentration in menstrual cycle, seizures occur. Similarly, in pre-menopause or menopause the menses stop and the level of reproductive hormones also reduce naturally. Then seizure's exacerbation also reduces. (Reddy D. S., Neurosteroids and Their Role in Sex-Specific Epilepsies, 2014).

Treatment:

There is no specified treatment for Catamenial epilepsy till now. But there are some hormonal and non-hormonal therapies available. A treatment scale therapy treatment trials should be conducted to know about the most reliable treatment for this disorder. (Alberto Verrotti, 2012).

Hormonal Treatment:

There is a need to study the role of steroids for the treatment of catamenial epilepsy. As hormonal concentration has a role in catamenial seizures so hormones can play an effective role in its treatment. In progesterone therapy different categories of progesterone are used, including naturally occurring progesterone and synthetic progesterone agents. (A.G. Herzog, 2012)

As progesterone has the anti-seizure effect that's why it is considered that progesterone and its metabolites can play a role in the CE treatment. For this purpose, natural progesterone the best option to treat CE. The absorption of progesterone is poor and short half-life. So, 100-200mg the dose uses orally two or three times a day. (Alberto Verrotti, 2012).

Natural progesterone

Cyclical natural progesterone use is effective for treatment of catamenial seizures. The dosage of 100-200 mg, 3 times a day is prescribed. Recommended to use in 15-28 day of the cycle. Three months treatment reduces the seizure's frequency by 54-68%. Antiseizure effects of progesterone is due to its metabolic conversion to neurosteroids. (Reddy D. S., 2007)

Cyclic progesterone:

Use of cyclical progesterone results in the significant reduction of catamenial seizures. In an investigation of women with catamenial exacerbation, 68% decline of seizures is observed over 3 months of observation. Progesterone is more effective when used regularly during the 2nd half of the cycle and discontinued after 3-4 days at the end of the menstrual cycle. Good recovery is observed in women who relied on cyclical

progesterone as compare to antiepileptic drugs. Natural progesterone can be used in variable dosage depending upon tolerability. Usually 25-200 mg should be taken thrice a day due to its low half-life. Overdosage may cause sedation, asthenia and emotional problems. These side effects can be lowered by changing dose. Progesterone usage and its effect on patient health should be monitored carefully. (Herzog, catamenial epilipsy: definition, prevalence, pathophisiology and treatment, 2008)

GnRH analog therapy:

GnRH analog is given intramuscularly after every 28 days which reduce the production of luteinizing hormone and estradiol. In GnRH analog treatment trials of Herzog et al 3.75mg dose of GnRH given to 10 women age between 20-50 years for about 11.8 months. After the complete trial the seizure's frequency decreased 50%, three became seizure free, duration of seizures became shorter in one patient and there was no effect on two patients. Before and after treatment of two months the level of serum estrogen and luteinizing hormone checked in one patient. It showed that the production of estrogen and LH had stopped. There were some side effects of this treatment. The menstrual cycle had stopped in all 10 women, and 8 women gained weight and effected by the headache. Some long-term effects of this treatment are osteoporosis and cardiovascular diseases. (Herzog, Hormonal Therapies: Progesterone, 2009).

Drug treatment:

Till date, no specific drug treatment prescribed for catamenial epilepsy, often intractable to some therapies. Different kinds of therapies are suggested, such as non-hormonal (antiepileptic drugs, acetazolamide or cyclical use of benzodiazepines) and hormonal therapies. But, the effectiveness of such treatments has not reported yet. Extensive trials required to mark an effectiveness of these treatments for catamenial epilepsy. (Alberto Verroti, 2012)

Some of the traditional and newer antiepileptic drugs are being used for treatment of seizures. However, these drugs may not fulfill the criteria of proper antiepileptic drugs. These drugs may cause inauspicious effects that may hurt the patient's lifestyle. We discussed here, some commonly used antiepileptic drugs that, play a vital role in management of catamenial seizures.

Acetazolamide

Acetazolamide is an effective inhibitor of carbonic anhydrase, an enzyme concerned for water balance in kidney and reabsorption of $NAHCO_3$. Acetazolamide used theoretically for the cure of catamenial seizures and refractory epilepsy. However, some women reported loss of tolerance and effectiveness while using acetazolamide.

Mederoxyprogesterone acetate

Mederoxyprogesterone acetate results in lower seizure frequency by 39% in women with catamenial epilepsy. It suppresses the seizures. The long-term use of Mederoxyprogesterone acetate may result in elimination of ovarian function. Moreover, treatment of Mederoxyprogesterone acetate may lead to overweight and spotting.

Benzodiazepines

Clonazepam and clobazam are the type of Benzodiazepines which shows positive modulation for GABA receptors and anti-seizure effect. The effectiveness of clobazam is considerable when treating the catamenial epilepsy. Clobazam may cause sedation and depression in the patient. The dosage of 5-10 mg/day is recommended. Disclosure to neuroactive steroids may affect the clinical utility of benzodiazepines. (Reddy D. S., 2007)

Discussion:

As epilepsy is a neuronal disorder that's why it effects the whole-body functioning. The main reason of menstrual seizures is the female's hormonal disturbance. When an epileptic patient experiences seizure then neuronal activity disturbs so hormonal disturbance is a normal thing in this patient. As females are already very sensitive to the exposure of these sex hormones. So, epileptic women have more disturbance in their hormonal concentration and experiences swear seizures. In our recent research survey, some non-epileptic females also feel minor seizures during or just before their menstruation. If we look the results of the survey, then there are only 3.6% females are epileptic patient. But 10.9% females feel seizures during or just before menstruation. Then definitely these seizures are also due to the varying concentration of their sex hormones during menstruation. But when we talk about an epileptic female then there is a swear imbalance in hormones due to an epileptic disorder. A normal non-epileptic female who is also feeling seizures then she may have hormonal disturbance due to some other reasons like hypertension, phobias, diets which imbalance her hormones. Then what will we say about the situation of non-epileptic women who are experiencing seizures. We will simply call it a hormonal disorder.

Recommendation:

This research will clear the concept of catamenial epilepsy because in our survey there are some non-epileptic women who are also experiencing seizures during menstruation. Epileptic and non-epileptic women experience same type of seizures which are partial seizures. So, if we consider catamenial epilepsy just in an epileptic woman then what about those non-epileptic women who also experience seizures during menstruation? This is the main question, according to the current definition of catamenial epilepsy that only an epileptic woman feels seizures.

References

A.G. Herzog, K. F. (2012). Progesterone vs placebo therapy for women with epilepsy: A randomized clinical trial. *Neurology*. doi: 10.1212/WNL.0b013e318259e1f9

Alberto Verroti, C. D. (2012). diagnosis and managment of catamenial seizures: a review. *international journal of women's health*, 535–541. doi:10.2147/IJWH.S28872

Alberto Verrotti, C. D. (2012). Diagnosis and management of catamenial seizures. *International Journal of Women's Health*, 535-541. doi: 10.2147/IJWH.S28872

Albi J. Chalissery, E. M.-W. (2017). Recurrent catamenial status epilepticus: Is it rare or an under recognized phenomenon in women with epilepsy? *Epilepsy & behavior case reports*, 19-21. doi: 10.1016/j.ebcr.2017.10.002

Andrew Herzog, T. F. (2004). Hormones and seizures. *Cleveland Clinic Journal of Medicine*, 11-18. doi: 10.3949/ccjm.71.suppl_2.s11

Deepak Kumar, S. I. (2020). The Frequency of Catamenial Epilepsy in Female Epileptic Patients of Reproductive Age Group Presented to the Tertiary Care Hospital. *cureus*, 1-3. doi:10.7759/cureus.11635

Eva Catenaccio1, W. M. (2016). Estrogen- and progesterone-mediated structural neuroplasticity in women: evidence from neuroimaging. *Brain structure & function*, 3-40. doi: 10.1007/s00429-016-1197-x

Herzog, A. G. (2008). catamenial epilipsy: definition, prevalence, pathophisiology and treatment. *Seizure*, 151-159. doi:10.1016/j.seizure.2007.11.014

Herzog, A. G. (2009). Hormonal Therapies: Progesterone. *Neurotherapeutics*, 383-391. doi: 10.1016/j.nurt.2009.01.009

Jessica Le, N. T. (2020). The Menstrual Cycle, and Premenstrual Disorders: A Review. *Brain sciences*, 2-14. doi: 10.3390/brainsci10040198

Kumar, A., Maini, K., Arya, K., & Sharma, S. (2021). *Simple Partial Seizure.* statperals.

mujahid, a. a. (2000). varoious . *springerr*.

Nancy Foldvary-Schaefer, T. F. (2003). Catamenial epilepsy: Pathophysiology, diagnosis, and management. *Neurology*. doi: 10.1212/wnl.61.6_suppl_2.s2

Naymeé J. Vélez-Ruiz, M. a. (2019). Issues for Women with Epilepsy. *Neurologic clinics*, 1. doi:10.1016/j.ncl.2015.11.009

Reddy, D. S. (2007). Perimenstrual catamenial epilepsy. *Women's health (London, England)*, 195-206. doi: 10.2217/17455057.3.2.195

Reddy, D. S. (2014). Neurosteroids and Their Role in Sex-Specific Epilepsies. *Neurobiology of disease*, 8-11. doi: 10.1016/j.nbd.2014.06.010

Reddy, D. S. (2014). Neurosteroids and Their Role in Sex-Specific Epilepsies. *Neurobiology of disease*, 198-209. doi: 10.1016/j.nbd.2014.06.010

Samuel Frank, N. A. (2020). A Clinical Approach to Catamenial Epilepsy. *PMC*.

Samuel Frank, N. A. (2020). A Clinical Approach to Catamenial Epilepsy. *The Permanente Journal*, 1-3. doi:10.7812/TPP/19.145

Suchitra Joshi, J. K. (2019). Neurosteroid regulation of GABAA receptors: a role in catamenial. *Brain research*, 10-11. doi:10.1016/j.brainres.2018.02.031

Yinhao Violet Wu, W. M. (2018). Progesterone, 5a-dihydropogesterone and allopregnanolone's effects on seizures: A review of animal and clinical studies. *Seizure*, 26-36. doi: 10.1016/j.seizure.2018.10.012