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SEIZURE OCCURRENCE AND HORMONAL CHANGES DURING MENSTRUAL CYCLE: PAST AND PRESENT PERSPECTIVES

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ABSTRACT

Epilepsy or epilepsies are the disorders of neuronal excitability. Mechanisms and pathophysiology of epilepsies have been reviewed and studies thoroughly. A variety of factors including electrolytes, hormones, water retention, and glucose etc. were investigated as changing the excitability without specific variations due to gender. A variety of causes for pathophysiology of menstrual/catamenial epilepsy were elucidated, e.g., decrease of progesterone levels in luteal phase, and change in estrogen and progesterone, basal body temperature (BBT) and sleeping-waking cycle, plasma calcium levels, cortical excitability and change in plasma gonadotropic hormones (luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin (PRL), plasma cortisol, feedback mechanisms involving hypothalamo-pituitary axis (HHPA), seizure occurrence associated with ionic calcium and other electrolytes, electrolytes and water metabolism, water retention/edema/ weight gain, psychic/emotional disorders and antiepileptic/antiseizure medication. Further studies are needed to have insight of the management of epilepsy and a variety of other related disorders. The present review provides information about the seizure occurrence, seizure types and frequency, pathophysiological factors, and mechanisms of the development of menstrual/catamenial epilepsy, associated conditions/ comorbidities, and management of catamenial seizures during menstrual cycle. Future research studies will hopefully uncover further information for seizure exacerbation with hormonal changes during perimenstrual, periovulatory and other segments/ phases in the menstrual cycle and will provide the better management of seizure disorders in women with menstrual/ catamenial epilepsy.

Keywords: Seizure occurrence, menstrual cycle, seizure frequency and types, menstrual/catamenial epilepsy, hormones, cycle segments/ cycle phases

INTRODUCTION

Epilepsy or epilepsies are the disorders of excitability disorders (Ngugi *et al*., 2010; Kansal *et al*., 2024; Al-Redouan *et al*., 2025). Mechanisms and pathophysiology of epilepsies have been reviewed and studies thoroughly (Delgado-Escueta *et al*., 1986; Dwyer *et al*., 1986; Hussain *et al*. 1987; Gloor, 1990; Haglund and Schwartzkroin, 1990; Hussain, 1991, 2010; Hoffman and Haberly, 1993;Aziz and Hussain, 1994a,b; Burneo *et al*., 2005; Hussain *et al*., 2006, 2007a, b; Pitkänen *et al*., 2007; Hansen *et al*., 2009; Kariyawasam *et al*., 2009; Cardarelli and Smith, 2010; Leppik and Birnbaum, 2010; Abachi, 2015; McKee and Privitera, 2017; Voinescu and Pennell, 2017; Chai *et al*., 2019; Frank and Tyson, 2020; Roeder and Leira, 2021; Liu and Chen, 2022; Kansal *et al*., 2022; Octaviana *et al*., 2022; Abachi *et al*., 2025; Abeysinghe *et al*., 2025; Alizadeh *et al*., 2025; Zeidan *et al*., 2025; Zhang *et al*., 2025). A variety of factors including electrolytes, hormones and glucose were investigated as changing the excitability with no specific variation due to gender (Burneo *et al*., 2005). Around 65 million people suffer world-over with the disorders of epilepsies (Ngugi *et al*., 2010).

A variety of causes for pathophysiology of menstrual/catamenial epilepsy (El-Khayat *et al*., 2008; Kariyawasam *et al*., 2009; Pennell, 2009; Herzog and Frye, 2014; Chalissery *et al*., 2019; Frank and Tyson, 2020; Zhao *et al*., 2025) were elucidated, e.g., decrease of progesterone levels in luteal phase (Rosciszewska *et al*., 1985; Herzog and Frye, 2014), estrogen and progesterone variations (Laidlaw, 1956; Backstrom, 1976), basal body temperature (BBT) and sleeping-waking cycle (Hussain, 1991), plasma calcium levels (Hussain, 1991; Hamed *et al*., 2004), cortical excitability and change in plasma gonadotropic hormones (luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin (PRL) (Hussain, 1991; Luef, 2010), plasma cortisol (Hussain, 1991; Marek *et al*., 2010), feedback mechanisms involving hypothalamo-pituitary axis (HHPA) (Rebar and Yen, 1979), seizure occurrence associated with ionic calcium and other electrolytes (Hussain *et al*., 1987; Jacono and Robertson, 1987, Hussain, 1991), electrolytes and water metabolism (Hussain, 1991; Castilla-Guerra *et al*., 2006; Reynolds *et al*., 2007), water retention/edema/ weight gain (McQuarrie, 1932) though not accepted by Ansell and Clarke (1956), psychic/emotional disorders (Stieglitz and Kimble, 1949) and antiepileptic/antiseizure medication (Hussain *et al*., 1987, 2007a; Kumar *et al*., 1988; Qureshi *et al*., 1988; Bonuccelli *et al*., 1989; Hamed *et al*., 2004).

One major aspect of the studies in epilepsy disorders associates with the endocrine and neuroendocrine changes during various phases/ segments of menstrual cycle especially the perimenstrual and periovulatory segments (Zimmerman, 1986; Hussain *et al*., 1987; Schachter, 1988; Hussain, 1991, 2010; Crawford, 2005; Hussain *et al*., 2006, 2007a; Harden, 2008; Pennell, 2009; Motta *et al*., 2013; Herzog and Frye, 2014; Joshi and Kapur, 2019; Frank and Tyson, 2020; Reddy, 2020; Roeder and Leira, 2021; Taubøll *et al*., 2021; Octaviana *et al*., 2022; Parekh *et al*., 2022; Sazgar *et al*., 2023; Alshakhouri *et al*., 2024; Rider *et al*., 2024; Eid *et al*., 2025; Niu *et al*., 2025).

Role of estrogen, progesterone and other steroid hormones during menstrual cycle in women with menstrual epilepsy were investigated comprehensively (Backstrom *et al*., 1985; Zimmerman, 1986; Hussain *et al*., 1987; Qureshi *et al*., 1988; Schachter, 1988; Hussain, 1991; Crawford, 2005; Tuveri *et al*., 2008; Kariyawasam *et al*., 2009; Motta *et al*., 2013; Herzog and Frye, 2014; Joshi and Kapur, 2019; Frank and Tyson, 2020; Taubøll *et al*., 2021; Octaviana *et al*., 2022; Parekh *et al*., 2022; Sazgar *et al*., 2023; Alshakhouri *et al*., 2024; Rider *et al*., 2024;) Niu *et al*., 2025. Some of the highly important studies in perimenstrual or pericatamenial pattern of seizures provided clear evidence for the seizures appearing perimenstrually (Hussain *et al*., 1987; Rosciszewska, 1987; Qureshi *et al*., 1988; Herzog *et al*., 1997; Hussain *et al*., 2006, 2007a; Herzog and Frye, 2014; Roeder and Leira, 2021).

Catamenial seizures were either generalized or focal (El-Khayat *et al*., 2008) or seizures in epilepsy syndromes/temporal lobe epilepsy (Morrel, 1999). However, controversial findings were documented for seizure types indicating catamenial pattern (El-Khayat *et al*., 2008; Kariyawasam *et al*., 2009; Pennell, 2009; Reddy, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021), since most of the previous studies were either conducted for generalized seizures (Laidlaw, 1956; Backstorm, 1976), or there was no mention of the type of seizures and other description (Ansell and Clarke, 1956; Bandler *et al*., 1957).

Some of the studies (Helmchen *et al*., 1964) described only the partial seizures associated with menstrual cycle with change in estrogen levels in ovulatory menstrual cycles, or the catamenial pattern of exacerbation was seen in generalized grand mal as well as complex partial seizures (Sanchez-Longo and Gonzales-Saldana, 1966), though the association of menstrual/catamenial epilepsy was evident more with partial epilepsy (specially the temporal lobe epilepsy) than the generalized epilepsy (Foldvary-Schaefer and Falcone, 2003).

Catamenial seizure defined by Gastaut (1973) was as: "An epileptic seizure that occurs either during menstruation or several days preceding or following it and that is caused by a lowering of the convulsive threshold secondary to endocrine and cellular changes brought about by menstruation". It was noted the various definitions had wide influence on collecting and interpreting the data (Herzog *et al*., 1997; Herzog *et al*., 2012). However, the definition of catamenial epilepsy developed by Gastaut (1973) is generally accepted (Hussain *et al*., 1987; Hussain, 1991, 2010; Herzog *et al*. 1997, 2004; Reddy, 2009; Herzog and Frye, 2014).

The terminologies of precatamenial or premenstrual epilepsy are employed synonymously for the epilepsy in women signifying premenstrual seizure exacerbations (increase in seizure frequency) mainly or almost exclusively few or several days prior to the start of the menstruation phase (Hussain, 1991, 2010). The term pericatamenial was specified where exacerbation in seizure occurrence was found aligned with almost all three pericatamenial phases (premenstrual, menstrual and postmenstrual) (Hussain, 1991; Hussain, 2010).

A term semi-pericatamenial/ partial pericatamenial was designated where mild or partial seizure exacerbation occurred in menstruation related phases/ segments/ days or perimenstrual related phases (Hussain, 1991; Hussain, 2010). The menstrual epilepsy or catamenial epilepsy was defined as an epilepsy type manifesting greater than the average frequency of seizure occurrence during perimenstrual period and periovulatory periods in normal ovulatory and anovulatory cycles (Herzog *et al*.,1997).

Hormones are mainly involved factors in the pathophysiology of menstrual or the catamenial epilepsy (Hussain *et al*., 1987; Jacono and Robertson, 1987; Rosciszewska, 1987; Qureshi *et al*., 1988; Hussain, 1991; Hussain *et al*., 2006, 2007a, b; El-Khayat *et al*., 2008; Kariyawasam *et al*., 2009; Pennell, 2009; Reddy, 2009; Hussain, 2010; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021).

SEIZURE OCCURRENCE IN MENSTRUAL CYCLE

The hypothalamo-hypophyseal-ovarian axis (HHO) is the regulatory center for the hormonal/ neurohormonal interplay during the menstrual cycle length of which normally remains in the range of 24 to 35 days (most commonly as 27-30). The follicular, ovulatory, luteal and prerimenstrual phases in the menstrual cycle are regulated by HHO (Herzog *et al*., 1997; Foldvary-Schaefer and Falcone 2003). The menstrual epilepsy presents increase in the seizure frequency mainly in perimenstrual and periovulatory phases and increased seizure frequency may appear during or around the ovulation, perimenstruation or other phase/ phases. (Hussain *et al*., 1987, 2006, 2007a; Hussain, 1991, 2010; Kariyawasam *et al*., 2009; Pennell, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020;

Roeder and Leira, 2021). In other words, the menstrual epilepsy or catamenial epilepsy shows cyclical exacerbation or increase of epileptic seizures during a certain phase/ phases of the menstrual cycle (Herzog 2008).

Study of women with perimenstrual or pericatamenial epilepsy is performed generally by collecting the data during certain days before, during and after the menstruation phase (Hussain *et al*., 1987, Qureshi *et al*., 1988; Hussain, 1991; 2010). Initially the studies carried out in women with epilepsy showed seizures only during and closely around the menstruation (Rosciszewska, 1987), later studies involved a number of criteria, and the epileptic seizures not related to menstruation were also studied (Bandler *et al*., 1957; Hussain *et al*., 1987, Hussain, 1991, 2010). In view of the later investigations, it became quite essential to properly diagnose the patients with menstrual epilepsy (Frank and Tyson, 2020; Kansal *et al*., 2024). Both the patients with partial and generalized seizures manifest the catamenial epilepsy (Rosciszewska, 1980; Backstrom *et al*., 1984) with intractable type appearing in certain specific phases or days in the cycle (El-Khayat *et al*., 2008; Pennell, 2009; Reddy, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021).

The literature in catamenial epilepsy reveals that seizures occur during menstruation (Kramer, 1977), around menstruation (Logothetis *et al*., 1959; Frank and Tyson, 2020), about two days prior to menstruation (Bunter and Rosciszewska, 1975), during both in menstruation and premenstruation (Ansell and Clarke, 1956; Laidlaw, 1956), during all perimenstrual phases with predominant seizure occurrence premenstrually (Hussain *et al*., 1987, Hussain, 1991; 2010).

Appearance of seizures in menstruation were also documented in some of the women (Rosciszewska, 1974, 1987). Seizure frequency decreased in luteal phase (during 14 to 16 days prior to menstruation) (Laidlaw, 1956), and seizure frequency increased 14-16 days after menstruation (Helmchen *et al*., 1964). The ovulatory and anovulatory cycles showed both periovulatory (around the mid-cycle days in anovulatory) as well as perimenstrual seizures (El-Khayat *et al*., 2008).

Occurrence of seizures during menstrual cycle was previously suggested as associated to cycle phases/ segments though without any specific relation of seizures with specific phases (Bandler *et al*., 1957). However, the menstruation related seizure exacerbations were documented as: 31 to 60% (Herzog *et al*., 2004; El-Khayat *et al*., 2008), 10 to 63% (Ansell & Clarke, 1956; 72%: Laidlaw, 1956), and two third of women patients (Rosciszewska, 1980). A previous report shows 10 to 78% prevalence of catamenial seizures (Schelp and Speciali, 1983; Taubøll *et al*., 1991). The highest seizure occurrence was estimated during perimenstrual stage or phases (Taubøll *et al*., 1991).

The term menstrual epilepsy or catamenial epilepsy was considered appropriate for describing the occurrence of seizures having association with menstrual cycle (Laidlaw (1956; Gastaut, 1973). It was found that epileptic seizures generally appear around the menarche period which predict its clear association with the menstrual cycle (Penfield and Jasper, 1954). This view was quite similar to a prior suggestion that seizure occurrence somehow associates with the periods before or during menstruation but quite rarely with the period after the cessation of menstruation (Wilson 1940). However, considering the mentioned criteria showed lower frequency of seizures of catamenial type (Kariyawasam *et al*., 2009). Another study found 75% seizure occurrence in premenstrual 10 days (Duncan *et al*., 1993). Another previous study used the term of menstrual epilepsy in those women manifesting maximum number of seizures during or after the menstrual phase (Wilson, 1940) described later (Penfield & Jasper, 1954).

Seizures were further associated with menstrual phase, sex and menstrual cycle (Lennox, 1955; Bandler *et al*., 1957; Temkin, 1971). A number of studies noted that the association of menstrual epilepsy exists with menstruation (Bouchet and Cazauveilh, 1826; Penfiled and Jasper, 1954; Lennox, 1955; Ansell and Clarke, 1956; Logothetis *et al*., 1959; Backstrom, 1976; Newmark and Penry, 1980; Laidlaw and Richens, 1982; Hussain *et al*., 1987; Rosciszewska, 1987; Reddy, 2004a; Pennell, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021), though the type and management of seizures and further details were not provided (Livingston, 1972).

It was noted that increased generalized grand mal seizures occurred in ovulatory as well as anovulatory cycles (Backstrom, 1976). Grand mal seizures occurred on day 6 and 22 in another study (Grudzinska and Rosciszewska, 1980). The tonic-clonic seizures were more cyclical in appearance in those patients manifesting more than one type of seizures (Rosciszewska, 1987). It was also documented that partial type of seizures had increased frequency in menstruation and before ovulation but decreased frequency in the luteal phase (Backstrom *et al*., 1984).

It is highly essential to plan for collecting the precise record of seizure occurrence and related variables during the menstrual cycle that gives the main information for having the diagnosis of catamenial epilepsy/ or menstrual epilepsy (Hussain, 1991; Herzog, 2006; Herzog and Frye, 2014; Frank and Tyson, 2020; Kansal *et al*., 2024).

First bleeding day of the menstrual cycle is considered as the first day of menstrual cycle in general studies and in studies related to seizure exacerbation in specific phase/ phases of the menstrual cycle (Hussain 1991; Reddy, 2009). Catamenial exacerbation of seizures has the premenstrual (C1), the periovulatory (C2), and the luteal (C3) dispersion/ or patterns (Herzog *et al*., 1997; Kariyawasam *et al*., 2009; Pennell, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021). The division of the menstrual cycle into four phases as: menstrual (days

−3 till +3), follicular (days +4 till +9), ovulatory (+10 till +16) and luteal (days +17 till −4) was done (Reddy, 2009). However, we classified in our earlier studies the perimenstrual segment of menstrual cycle for non-catamenial and catamenial seizures as -1 to -4 for the premenstrual phase, 1 to 5 (depending on the duration of menstruation) for menstrual phase and +1 to +4 for the postmenstrual phase (Hussain *et al*., 1987; Hussain, 1991).

It has been suggested to have two or more consecutive menstrual cycles with two times or even greater increased number of seizures appearing in certain cycle-phase for its consideration as the catamenial seizure pattern (Reddy, 2009; Herzog 2015; Frank and Tyson, 2020). Seizure analysis during various parts in the menstrual cycle helped classifying the cycle into various segments/ specific phases (Hussain *et al*., 1987; Hussain, 1991, 2010). Besides the perimenstrual segment in menstrual cycle, the other important segment is periovulatory segment (El-Khayat *et al*., 2008).

Semi/partial precatamenial, semi/partial catamenial, semi/partial postcatamenial and other related terms were introduced based on the seizure dispersion or seizure pattern (Hussain *et al*., 1987; Hussain, 1991, 2010). Epilepsy was termed respectively as the "pubertal epilepsy" and the catamenial epilepsy if seizures occur during puberty period and perimenstruation (Gastaut,1973). Later investigation confirmed the various forms of epilepsy in women in their puberty, premenopause/postmenopause and during pregnancy (Rosciszewska,1987).

Exacerbation, and exacerbation pattern of the cycle-phase and cycle-segment seizures, and their types and frequency of occurrence are managed by several ways. The present article describes the seizure occurrence and hormonal variations and their association to understand the pathophysiology and management of the women subjects using antiepileptic/ antiseizure drugs, behavioral procedures and other approaches based on the association of the level of steroid and protein hormones and seizure frequency. Hopefully, the further studies would clarify and provide more appropriate information for the mechanisms of occurrence of exacerbation patterns in women especially with perimenstrual and periovulatory epilepsy.

ESTROGEN, PROGESTERONE AND EPILEPSY IN WOMEN

Seizure occurrence associates or does not associate with a specific cycle phase. Seizures unrelated to any cycle phase or segment (menstruation related or ovulation related) were termed as noncatamenial seizures (Hussain *et al*., 1987). It was noticed that rapid increase in the occurrence of seizures accompanied the decreased plasma levels of progesterone and increased levels of estradiol during menstruation related cycle segment (perimenstrual phases) (Hussain, 1991; Hussain, 2010). However, another report revealed decrease in estrogen (Herzog *et al*., 1997).

On the other hand, plasma progesterone was found unchanged but rapid and increased levels of plasma estrogen were obtained in women with double frequency of periovulatory seizures (Navis and Harden, 2016; Frank and Tyson, 2020). It was found that increased levels of estrogen during preovulation and the increased estrogen/progesterone ratio during the inadequate luteal phase associates with increased frequency of seizures (Reddy, 2009). It was found that the number of seizures correlated positively with the estrogen/progesterone ratio, and negatively with the progesterone levels (Backstrom, 1976; Rosciszewska, 1987).

It is important to know about the relatedness of endocrine/ neuroendocrine variations with the dispersion pattern of seizures during the menstrual cycle for establishing the criteria of catamenial pattern for diagnosing the catamenial epilepsy (Kariyawasam *et al*., 2009; Pennell, 2009; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021). Furthermore, the changes in seizure occurrence in ovulatory and anovulatory cycles can be explained with the help of understanding the neuroactive properties of estrogen and progesterone and serum levels of these steroid hormone (Herzog and Fowler, 2008; Herzog and Frye, 2014; Frank and Tyson, 2020). Very high doses of estrogen may increase, and very low doses of estrogen may decrease the epileptic activity (Zhang *et al*., 2015).

Estrogens comprise a protective effect (Velísková *et al*., 2010), and role of delaying the time of the onset of the occurrence kainite induced seizures (Velísková *et al*., 2000). Both menstrual cycle and steroidal hormones are affected by the seizures and antiepileptic drugs (AEDs) (Morrell and Montouris, 2004; Kariyawasam *et al*., 2009; Voinescu and Pennell, 2017; Frank and Tyson, 2020). Ovulatory cycles in subjects with generalized as well as partial seizures showed increased estrogen-progesterone ratio correlating with increased seizure occurrence (Backstrom, 1976). Some women may have certain menstrual abnormalities (Bosak *et al*., 2018) during e.g., anovulation. Specific procedures were employed for evaluating the catamenial change in seizure occurrence (Tuveri *et al*., 2008), though using a wide variety of methods for assessing the catamenial influence might not be the most appropriate approach.

Clinical and experimental studies (Abbas *et al*., 1995; Inam *et al*., 1995; Khan *et al*., 1995; Masood *et al*., 1995; Isojärvi *et al*., 2005) verified metabolic effects of estradiol. Estrogen showed aggravated response for the occurrence of seizures in patients with epilepsy (Logothetis *et al*., 1959). Studies in catamenial and non-catamenial patterns of seizures revealed decline in urinary excretion of estradiol, estriol as well as pregnanediol in women with catamenial

epilepsy only (Buntner & Rosciszewska, 1975), whereas no consistent of hormonal excretions were investigated as some reports presented excretion of pregnanediol and estrogen in patients having only catamenial pattern of seizures; and excretion of estrogen in women with both types of patterns (catamenial as well as non-catamenial) (Thirty *et al*., 1954; Zaichkina, 1963)

Ovariectomized female rats presented that estrogen changes the acquisition for seizures kindled by repeated stimulation of amygdala or by administration of pentylenetetrazol (PTZ) (Hom and Buterbaugh, 1986). It was further investigated that low dose of estradiol has neuroprotective action (Veliskova and Velisek, 2007; Velísek and Velísková, 2008). Convulsions were facilitated by the administration of estrogen in kindling model of epilepsy (kindling model was introduced by Graham Goddard, 1967), and other studies revealed hippocampal excitability and audiogenic seizures in animals that suggested the proconvulsant or convulsant actions (Logothetis *et al*., 1959; Wooley and Timiras, 1962a; Backstrom, *et al*., 1985; Hussain *et al*., 1987, 2006; Hussain, 1991, 2010).

Though convulsant effects of estrogen and anticonvulsant effects of progesterone were noticed in initial studies (Logothetis *et al*., 1959; Backstrom, *et al*., 1985), the later studies could not find the estrogen effects as proconvulsant or convulsant (Rosciszewska *et al*., 1986; Rosciszewska 1987). Ionized calcium was found negatively associated with estradiol levels in women with epilepsy (Jacono and Robertson, 1987).

A variety of actions/ functions of estrogen comprise increased glutamatergic excitatory transmission by N-methyl-D-aspartate (NMDA) receptors via mediation of kainite for activating glutamate receptors (Smejkalova and Woolley, 2010), and producing hyperexcitability (Herzog, 2015). The estradiol is synthesized by cytochrome aromatase, and the estradiol concentration in hippocampus elevates as compared to estradiol serum level (Hojo *et al*., 2009). The subjects with overweight status and obesity relating to estradiol concentrations in women of child-bearing age and associated with infertility/related disorders may present other disorders related to epilepsy and due to the use of antiepileptic drugs (AEDs) (Isojärvi *et al*., 2005; Rehman *et al*., 2012a, b, 2013a, b, c, d, 2016).

Correlation of the levels of progesterone in brain and serum explains that progesterone may cross blood-brain barrier (BBB) swiftly (Stoffel-Wagner 2001) and hence progesterone inhibits the seizure development and seizure occurrence (Holmes and, Weber 1984). It was suggested that the deficiency of progesterone occurs in inappropriate luteal phase in anovulatory cycles (Herzog *et al*., 1997). Progesterone manifested anticonvulsant/or antiepileptic effects in animal models as well as human studies (Logothetis *et al*., 1959; Backtrom *et al*., 1984, 1985; El-Khayat *et al*., 2008; Tuveri *et al*., 2008). The mid-luteal seizures decrease in number owing to increased levels of progesterone (Laidlaw, 1956; Backstrom, 1976), and seizures may increase close to menstrual period due to low levels of progesterone (Laidlaw, 1956).

Intravenous administration of progesterone showed significantly reduced spike frequency (Backstrom, 1984). On the other, declined levels of progesterone allows the gonadotropin-releasing hormone to increase for the generation of a next menstrual cycle (Foldvary-Schaefer and Falcone 2003; Reddy 2009). Progesterone may act: by slow and long post-transcriptional processes/mechanisms, by gamma aminobutyric acid receptor A ($GABA_A$) receptors that produces the effects of allopregnanolone, by sulfated progesterone metabolites for decreasing GABAergic neurotransmission, and hence elevating excitability, by activating progesterone receptors in the last days of luteal phase for elevating glutamatergic excitatory transmission that leads to the occurrence of perimenstrual seizures, and by causing the conversion of allopregnanolone and other neurosteroids for influencing brain receptors (Joshi *et al*., 2018; Joshi and Kapur, 2018, 2019; Kapur and Joshi, 2021; Shiono *et al*., 2021).

Progesterone effects by other ways via decreased levels of progesterone and allopregnanolone in the last luteal days for increasing the excitability, by the influence of allopregnanolone for elevating $GABA_A$ inhibitory effects, and via progesterone that has protective effect and maximum inhibition level against seizures owing to maximum levels of progesterone and allopregnanolone during mid-luteal phase (Reddy *et al*., 2001; Reddy 2004 a; Reddy 2022). Formation of 5α-dihydroprogesterone has been suggested an important factor for inhibiting neuronal excitability (Wu and Burnham, 2018)

LH, FSH, PRL AND CORTISOL IN MENSTRUAL EPILEPSY

The concentration of serum/ plasma luteinizing hormone (LH) and follicle stimulating hormone (FSH) vary according to gender (Kuba *et al*., 2006). The LH and FSH were found abnormally altered in epilepsy women patients with reproductive disorders (Hamed *et al*., 2004). The post-puberty increase in LH levels in subjects taking valproic acid and carbamazepine except decreased levels of LH after carbamazepine in the initial year, and elevation in LH levels in untreated patients while compared to control healthy subjects were some of the main observations (Isojarvi, 1990).

Variations in estradiol and FSH associated with lamotrigine and valproic acid, and irregular cycles with clobazam with polytherapy were observed (Octaviana *et al*., 2022). The LH levels verified the decreased levels of

progesterone in luteal but not in follicular phase (Rosciszewska *et al*., 1985; Hussain, 1991, 2010; Hussain *et al*., 2006).

However, it was notices that the concentration of LH-RH (luteinizing hormone releasing hormone) declined after using carbamazepine for about two months, whereas abnormal secretion of LH occurred in women with epilepsy, but the seizure frequency associated with the LH levels (Morrell, 1999). There are other reports that present change in LH pulse frequency (Bauer, 2001), increase in LH concentration in women patients with epilepsy (Rosciszewska *et al*., 1985), and even significant LH increase in catamenial epilepsy (Hussain, 1991, 2010).

Increased levels of LH and FSH were obtained after partial as well as generalized tonic-clonic seizures (Luef, 2010), epilepsy women with menstrual disorders and increased level of BMI and electroshock convulsions (Prabhakar *et al*., 2007). The disturbance in the secretions of gonadotropic hormones in epilepsy is considered happening under the influence of hypothalamo-pituitary-ovarian (HPO) axis involving neuroendocrine mechanisms (Sazgar *et al*., 2023).

There are several studies indicating increased levels of prolactin in women with menstrual or catamenial epilepsy (Hussain, 1991, 2010; Bauer, 2001; Hamed *et al*., 2004), directly correlating with seizure frequency as well as reproductive disorders (Isojarvi, 1990; Hamed *et al*., 2004); Luef, 2010). A report reveals lower concentration of estradiol and prolactin in women with epilepsy having higher frequency of seizure occurrence (Octaviana *et al*., 2022).

Cortisol is generally considered as differential marker for the proper diagnosis of epileptic seizures and psychogenic non-epileptic seizure types (Rider *et al*., 2024). The levels of cortisol are generally increased with the occurrence of seizures and especially in women with epilepsy, and under antiepileptic medication (Hussain, 1991, 2010; Marek *et al*., 2010; Rider *et al*., 2024).

Other studies show no significant variations of cortisol (Isojarvi, 1990), and decreased level of the ratio of dehydroepiandrosterone sulfate (DHEAS)/cortisol during perimenstrual phases in women with catamenial epilepsy (Tuveri *et al*., 2008). General studies about the pathophysiological role of cortisol showed increased serum/ plasma levels of cortisol after the occurrence of spontaneous epileptic seizures (Hussain, 1991, 2010; Marek *et al*., 2010; Rider *et al*., 2024), and under the influence of antiseizure medication.

OTHER FACTORS AND ASSOCIATED CONDITIONS

Water metabolism, water retention and serum level of water in catamenial epilepsy with / without medication (Hussain 1991, 2010; Shah *et al*., 2001; Frank and Tyson, 2020) revealed the involvement of water retention. Extracellular water storage is not considered responsible for seizure exacerbation (Ansell and Clarke, 1956), but water retention/ weight gain or edema was found partly responsible for premenstrual catamenial epilepsy (Hussain 1991, 2010). Overhydration is considered a factor leading to generalized tonic-clonic seizures and well treatable by increasing osmolality level (Saly and Andrew, 1993). Decrease in ionized calcium has also been documented causing seizures in women during menstrual cycle (Glasser and Levy, 1960).

Most of the studies in menstrual epilepsy relate to involvement of steroid and other hormones (Frank and Tyson, 2020; Roeder and Leira, 2021). Acetazolamide presented efficacy in menstrual epilepsy (Lim *et al*., 2001). A report shows that lamotrigine is not associated with causing weight-gain in catamenial epileptics (Morrell *et al*., 2003). However, more studies are required to be carried out for understanding the role of water metabolism and effect of medication in exacerbating the menstrual cycle related seizures. Serum sodium was found increased owing to electrolyte disturbances, valproate (Castilla-Guerra *et al*., 2006), long term antiepileptic medication (Hamed *et al*., 2004), combined therapies (Jallon and Picard, 2001), increased BMI, metabolic effects in response to insulin sensitivity (Reynolds *et al*., 2007).

Significant linear association of body weight with menstruation related disturbances was observed in women with generalized epilepsy but with no linear correlation of weight change with reproductive hormones/ or other menstrual disturbances (Prabhakar *et al*. 2007). It was generally suggested that hormones (gonadosteroidal, adrenosteroidal), anticonvulsant medication, electrolyte and water metabolism and other related factors are involved in women with epilepsy having catamenial pattern of seizures (Ansell and Clarke, 1956; Backstrom, 1976; Tuveri *et al*., 2008).

A number of changes occur with the occurrence of seizures or facilitating the occurrence of seizures. e.g.,: sleep wake cyclical changes (Ogihara *et al*., 2010), systemic influence of seizure occurrence and antiepileptic drugs (Shah *et al*., 2001; Hamed *et al*., 2004), increased basal body temperature (BBT) (Hussain, 1991; Ogihara *et al*., 2010), and extracellular potassium/ calcium response/calcium influx in paroxysmal depolarization shift after pentylenetetrazol effect (Luecke and Speckmann (1990), epilepsy as a risk factor in patients with ischemic stroke and other neurological conditions with epilepsy (Hussain *et al*., 1987; Hussain, 1991; Khan *et al*., 2009; Naz *et al*., 2009; Hussain, 2010; Roeder and Leira, 2021), serum calcium in the occurrence of seizures (Hamed *et al*., 2004), change

in the levels of sodium, potassium, calcium, and accumulating extracellular potassium, and inactivation of potassium currents/ potassium channels in epileptogenesis (Swann *et al*., 2000), negative correlation of estrogen with ionized calcium leading to catamenial exacerbation pattern (Jacono and Robertson, 1987), alpha-actinin in the menstrual cycle related to epileptogenesis and its increased property for transient receptor potential-3 (TRP-3) channels (Li *et al*., 2007; Mohandass *et al*., 2020; Sbai *et al*., 2020), variations in endogenous steroids e.g., progesterone metabolites via GABA(A) receptor (GABAR) mediation resulting to premenstrual disorders and catamenial epilepsy (Smith *et al*., 2007), sexual and reproductive endocrinological changes for testosterone and progesterone in men and women having epilepsy and other complications (Smith *et al*., 2007; Hussain *et al*., 2017; Demirkhanyan *et al*., 2018; Mohandass *et al*., 2020; Lemley and Voinescu, 2023), oxidative stress/ lipid profile variations under the pharmacological effect in experimental hypercholesterolemia (Fatima *et al*., 2007) and patients with intractable epilepsy (Shawki *et al*., 2013), and several other changes (Khan and Hussain, 2008; Sohail and Hussain, 2008, 2009, 2013; Yasmeen *et al*., 2008, 2009; Sohail *et al*., 2013, 2019) that may accompany with other reproductive problems (Lemley and Voinescu, 2023).

There are clinical conditions related to common cold developing to epileptic seizures (Jallon *et al*., 1986; Anjum and Hussain, 1998 a, b; 1999 a, b, c, d, e; Mahmood and Hussain, 1998, 1999; Munir and Hussain, 1999; Takahashi *et al*., 2003; Fujita *et al*., 2011; Hussain and Hussain, 2020; Neshige *et al*., 2023). A report shows generalized seizures occurring after common cold that could not be managed for the seizures associated to host immune system discomfort (Takahashi *et al*., 2003). The pneumonia (Ahmed *et al*., 1994) might also get accompanied with seizures and ARDS (acute respiratory distress syndrome) (Saito *et al*., 2013).

Hypertension occurs due to a number of etiological factors (Siddiqui *et al*., 1994) but it can lead to seizures and could be managed by employing low dosages of combined estrogen-progestin-oral contraceptives in women having menstrual epilepsy (Presl, 1991). Sex-related/ hormone related disorders e.g., exacerbation pattern of seizures, viral/bacterial infections of skin/cosmetic problems (Inam *et al*., 1994) effect hair/skin after the use of antiepileptic drugs (Røste and Taubøll, 2007).

A variety of conditions/ comorbidities associate or appear with the epilepsy and antiepileptic medication. In view of significantly heightened erythrocyte osmotic fragility in certain conditions (Zafar *et al*., 1990) including epilepsy subjects as compared to healthy control subjects, adding the antioxidants with antiepileptic medication proved beneficial (Yalçin *et al*., 1994). The biochemical/physiological and immune factors associate with cerebrovascular, immune and epilepsy disorders (Hussain and Hassan, 1982; Breckwoldt *et al*., 1990; Hussain, 2022 a, b, 2024 a, b). The kisspeptin that appears low in infertility (Mumtaz *et al*., 2016) decreases the excitability associated with the use of antiepileptic drugs for treating the patients with intractable epilepsy (Buffel *et al*., 2015).

The density functional theory (DFT) for epimeric and anomeric structural complexities (Ahmadi *et al*., 2017) have provided insights via studying reproductive steroid hormones to understand the cyclical changes (Liang *et al*., 2024) and epileptic disorders (Singh and Pathak, 2024). While sodium channel mutations causing epilepsy (Meisler and Kearney, 2005), interactive studies to understand the hydrogen bonding in sodium channels have revealed epileptopharmacological and epileptoelectrophysiological aspects in the mechanisms of epilepsies (Ahsan, 2013; Hussain 2022 a, 2024 a).

The depot medroxyprogesterone acetate, Depo-Provera or DMPA as a contraceptive showed decreased sperm penetration, estrogen related disorders, and decreased seizure frequency in epilepsy, with a side effect of causing weight gain (Khoiny *et al*., 1996; Rehman *et al*., 2014, 2015). It is known that transient-receptor potential (TRP) channels besides being related to kidney diseases (Wu *et al*., 2006) are involved epilepsy disorders (Matsubara *et al*., 2021; Zhao and Rohacs, 2021).

ANTIEPILEPTIC DRUGS AND OTHER MANAGEMENT ASPECTS

A study was conducted quite comprehensively for women with epilepsy receiving the treatment or not (Kariyawasam *et al*., 2009; Voinescu and Pennell, 2017; Herzog and Frye, 2014; Frank and Tyson, 2020; Roeder and Leira, 2021). No positive evidence could be obtained for the anti-estrogen products used for catamenial epilepsy patients with the treatment of catamenial patterns of seizures (Herzog, 1988), though based on the data of premenstrual catamenial epilepsy, it was suggested to use anti-estrogen products that may cause decrease in the premenstrual seizures (Hussain, 1987; Qureshi *et al*., 1988; Hussain, 1991, 2010). Furthermore, the interaction of first-line antiepileptic monotherapy drugs with estrogen is altered while attempting to control seizures in women with epilepsy (Grover *et al*., 2012)

Progesterone was suggested to the women patients having seizure exacerbation perimenstrually (Herzog *et al*., 2012). A later investigation indicated the effects of progesterone in seizures during perimenstruation (negative correlation of progesterone with seizure frequency) (Herzog and Frye, 2014). Gonadosteroid hormones and

anticonvulsant drugs that are metabolized via involvement of cytochrome P450-a liver enzyme, show that the blood levels remain changing and anticonvulsant efficacy is decreased (Patel and Foldvary-Schaefer, 2014).

Concentration of steroid hormones under the treatment of carbamazepine in epilepsy subjects remains fluctuating (Isojarvi, 1990). Some of the antiepileptic drugs cause decline in the effectiveness/efficacy of oral contraceptive activity (Harden and Leppik, 2006; Velísková, 2007) and may lead to gonadosteroid-related disorders. Hence, it seems necessary to carry out further related studies to have insight of the interactive association for contraceptives, gonadosteroids and antiepileptic drugs.

Furthermore, it was found that non-enzyme-inducing antiepileptic drugs usually do not cause the disorders that are caused by enzyme inducing antiepileptic drugs on the metabolism of steroidal hormones and contraceptives (Isojarvi *et al*, 2005). The women subjects having intractable/ drug-resistant perimenstrual seizures showed efficacy of gonadotropic releasing hormone (Bauer *et al*., 1992).

Hormonal/ non-hormonal conventional drugs did not present beneficial and reliable effects in catamenial epilepsy women (Patel and Foldvary-Schaefer, 2014). Clobazam, lamotrigine, acetazolamide and various other products were used. Several side effects were noticed for clobazam ($GABA_A$ receptor modulator), lamotrigine (sodium channel blocker showing EEG changes corresponding to efficacy) and accetazolamide (carbonic anhydrase inhibitor), but these products showed efficacy for catamenial seizures (Lim *et al*., 2001; Gilad *et al*., 2008).

Furthermore, based on systemic studies in cycle phases in women with menstrual/catamenial epilepsy and non-catamenial epilepsy (Rosciszewska *et al*., 1986; Hussain *et al*., 1987, 2006, 2007; Frank and Tyson, 2020), drug products were developed based on activity of neurotransmitters mainly the gamma amino butyric acid (GABA) since reduced inhibitory neurotransmission was noticed in epilepsy including seizure exacerbation in the luteal segment/ phases and decreased levels of phenytoin levels in menstruation in women with menstrual/catamenial epilepsy and beneficial effects of clomiphene especially in women with various reproductive disorders and partial seizures (Herzog, 1988; Maguire and Nevitt, 2021). Lower levels of phenytoin correlated with the exacerbation of perimenstrual seizures (Rościszewska *et al*., 1986).

Various treatment methodologies and approaches were employed for the seizure disorders in women to manage the catamenial exacerbations. Ochratoxin contamination in the feed of broilers (Zafar *et al*., 2001) in high concentration may cause head nodding syndrome considered as an epileptic manifestation (Echodu *et al*., 2018).

The previous psychological and behavioral studies revealed that the efficacy of the muscle stimulation leading to muscle fatigue-related to progressive relaxation therapy /exercises (Hussain, 1983; Akgün Şahin and Dayapoğlu, 2015) and is considered efficacious (Jacobson 1927, 1929, 1938; Canter *et al*., 1975; Rousseau *et al*., 1985). Later studies by employing modified progressive relaxation (MPR) therapy (Hussain 1982, 1984, 1994, 2001) demonstrated such and other effects. Furthermore, the cannabidiol model and liposomal models were found quite efficacious for seizure disorders via itraconazole, and other products (Matias *et al*., 2017; Eh *et al*., 2021; Yeung *et al*., 2023).

Further studies are needed to have insight of the management of epilepsy and a variety of other membrane-related disorders (Matias *et al*., 2017). Future research studies will hopefully uncover further information for seizure exacerbation with hormonal changes during perimenstrual, periovulatory and other segments/ phases in the menstrual cycle, and the better management of seizure disorders in women with menstrual/ catamenial epilepsy.

CONCLUSIONS

The present review provides information about the seizure occurrence, seizure types and frequency, pathophysiological factors, and mechanisms of the development of menstrual/catamenial epilepsy, associated conditions/ comorbidities, and management of catamenial seizures during menstrual cycle. Future research studies will hopefully uncover further information for seizure exacerbation with hormonal changes during perimenstrual, periovulatory and other segments/ phases in the menstrual cycle and will provide the better management of seizure disorders in women with menstrual/ catamenial epilepsy.

DEDICATION

The author dedicates this article to the loving memory of his highly intellectual mentor and the Ph.D. research guide - the Late Prof. Emeritus Hasan Aziz, FRCP (Lond), FRCP (Edin), (1939 – 2022) who served as Professor and Head of the Department of Neurology, Director Jinnah Postgraduate Medical Centre (JPMC), Chairman Academic Council, JPMC and Emeritus Professor of Neurology. Professor Dr. Hasan Aziz was a marvelous teacher and excellent mentor of the author in 1980's and 1990's in the areas of Clinical Neurology, Electrophysiology, Neurophysiology, Neurological Physiology, Endocrineurology, Neuroendocrinology, Cellular and Molecular Neurology/ Neurobiology, Biophysics, Epileptology and Neuroscience in general.

The author was lucky to have the great guidance of Dr. Hasan Aziz, initially in the Epilepsy Clinic (OPDs) and EEG (Electroencephalography) Lab, Department of Neuropsychiatry (later the Department of Neurology) and in the areas of the diagnosis, pathophysiology and management of women with Catamenial Epilepsy (epilepsy in women associated with segments/ phases of the menstrual cycle) and related neurological diseases. It is so sad that the author promised in 2021 with Prof Hasan Aziz for collaborative research in the Kindling Model of Epilepsy in rat/ mice and other Experimental Studies in Epileptology/ Neurology/ Neuroscience but could not get opportunity due to being away from the country and sudden death of the Honorable Guide.

He was a true scholar with a deep interest in literature, poetry and classical music/Qawwali. His seminal compilation and translation of Sufi poetry in the book entitled, 'Kalaam-e-Aarifaan', will continue to give for all times to come, just like all his other projects. A gentle and caring human being, an excellent teacher, and a mentor par excellence. Even more so, a kind and generous human being, who left a mark on every soul whose life he touched.

Late Prof. Hasan Aziz
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