

## 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 studied 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

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### 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 studied 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 worldwide 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 premenstrual 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; Penfield 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 (Roszczewska, 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; Roszczewska, 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; Velisek 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; Backstrom *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<sub>A</sub>) 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<sub>A</sub> 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 5 $\alpha$ -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 (Isojärvi, 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 (Roszczewska *et al.*, 1985; Hussain, 1991, 2010; Hussain *et al.*, 2006).

However, it was noticed 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 (Roszczewska *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 (Yalçın *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 (Khojiny *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<sub>A</sub> receptor modulator), lamotrigine (sodium channel blocker showing EEG changes corresponding to efficacy) and acetazolamide (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, Endocrinology, 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.



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## REFERENCES

- Abachi, H. (2015). Parasomnia. *Nihon Rinsho.*, 73(6):949-53.
- Abachi, H., K. Nishida and N. Futamura (2025). Natural History and Progression of Dentatorubral-Pallidolusian Atrophy (DRPLA): A Retrospective Study of 22 Patients. *Mov Disord Clin Pract.*, doi: 10.1002/mdc3.70088.
- Abbas, K., N. Khan, S. Inam, S. Masood and Z. Hussain (1995). Influence of estradiol valerate on plasma phospholipids in *Uromastix hardwickii*. *First National Conference on Pharmacology and Therapeutics*. Faculty of Pharmacy, University of Karachi, P: 43.
- Abeyasinghe, R., S. Tao, S.D. Lhatoo, G.Q. Zhang and L. Cui (2025). Leveraging pretrained language models for seizure frequency extraction from epilepsy evaluation reports. *NPJ Digit Med.*, 14;8(1):208. doi: 10.1038/s41746-025-01592-4.
- Ahmed, N., Z. Hussain, S. Inam and S. Masood S (1994). Recent advances in clinical diagnosis and treatment of pneumonia. *Advances in Clinical Medicine*, p: 5-7.
- Ahmadi, S., V.M. Achari, Z. Hussain and R. Hashim (2017). Epimeric and anomeric relationship of octyl-  $\alpha$  -D-glucosyl/galactosides: insight from density functional theory and atom in molecules studies. *Computational and Theoretical Chemistry* (Amsterdam: Elsevier), 1108: 93–102.
- Ahsan, M.J. (2013). Semicarbazone analogs as anticonvulsant agents: a review. *Cent Nerv Syst Agents Med Chem*, 13(2):148-58.
- Akgün Şahin, Z and N. Dayapoğlu (2015). Effect of progressive relaxation exercises on fatigue and sleep quality in patients with chronic obstructive lung disease (COPD). *Complement Ther Clin Pract*, 21(4):277-81.
- Alizadeh, P., A.J. Babadi, N. Ghadiri, M. Neissi and M. Zeinali (2025). Gene variant analysis in pediatrics with early-onset epilepsy: Identification of novel variants. *Pract Lab Med.*, 45:e00462. doi: 10.1016/j.plabm.2025.e00462.
- Al-Redouan, A., A. Busch, M. Salaj, H. Kubova and R. Druga (2025). Dorsal Striatum Is Compromised by Status Epilepticus Induced in Immature Developing Animal Experimental Model of Mesial Temporal Lobe Epilepsy. *Int J Mol Sci.*, 26(7):3349. doi: 10.3390/ijms26073349.
- Alshakhouri ,M., C. Sharpe, P. Bergin and R.L. Sumner (2024). Female sex steroids and epilepsy: Part 1. A review of reciprocal changes in reproductive systems, cycles, and seizures. *Epilepsia*, 65(3):556-568.
- Anjum, S. and Z. Hussain (1999 a). Common cold-upper respiratory infection. *The Medicine International*, 2 (1): 5-7
- Anjum, S. and Z. Hussain (1999 b). Diagnostic features in common colds. *The Medicine International*, 2 (2): 10-12
- Anjum, S. and Z. Hussain (1999 c). Rhinovirus and common colds. *The Medicine International*, 2 (4): 8-10
- Anjum, S. and Z. Hussain (1999 d). Age of children and common colds. *The Medicine International*, 2 (11): 6-8
- Anjum, S. and Z. Hussain (1999 e). Complications in common colds. *The Medicine International*, 2 (12): 5-7
- Anjum, S. and Z. Hussain (1998 a). How do common colds spread? *The Medicine International*, 1 (2): 9-12.
- Anjum, S. and Z. Hussain (1998 b). Cellular and molecular pathophysiology of common colds. *The Medicine International*, 1 (6): 2-4.
- Ansell, B. and E. Clarke (1956). Acetazolamide in treatment of epilepsy. *Br Med J.*, 1(4968): 650-654.

- Aziz, H. and Z. Hussain (1994a). Neonatal seizures- Diagnosis and treatment. In: *Biological Foundations of Medicine*. PAASK, Karachi, p:5-9.
- Aziz, H. and Z. Hussain (1994b). Recent advances and future perspectives in epilepsy-A Review. In: *Advances in Clinical Medicine*, PAASK Karachi, p:8-14.
- Backstrom, T. (1976). Epileptic seizures in women related to plasma estrogen and progesterone during the menstrual cycle. *Acta Neurol Scand*, 54(4):321-347.
- Backstrom, T., M. Bixo and S. Hammarback (1985). Ovarian steroid hormones. Effects on mood, behaviour and brain excitability. *Acta Obstet Gynecol Scand Suppl*, 130:19-24.
- Backstrom, T., B. Zetterlund, S. Blom and N. Romano (1984). Effects of intravenous progesterone infusions on the epileptic discharge frequency in women with partial epilepsy. *Acta Neurol Scand*, 69 (4): 240-248.
- Bandler, B., I.C. Kaufman, J.W. Dykens, M. Schleifer and L.N. Shapiro (1957). Seizures and the menstrual cycle *Am J Psychiat*, 113(8): 704-708.
- Bauer, J. (2001). Interactions between hormones and epilepsy in female patients. *Epilepsia*, 42Suppl 3:20.
- Bauer, J., L. Wildt, D. Flügel and H. Stefan (1992). The effect of a synthetic GnRH analogue on catamenial epilepsy: a study in ten patients. *J Neurol*, 1992 May;239(5):284-6.
- Bonuccelli, U., G.B. Melis, A.M. Paoletti, P. Fioretti, L. Murri and A. Murtorio (1989). Unbalanced progesterone and estradiol secretion in catamenial epilepsy. *Epilepsy Res.*, 3(2):100-106.
- Bosak, M., A. Slowik, and W. Turaj (2018). Menstrual disorders and their determinants among women with epilepsy. *Neuropsychiatr Dis Treat*, 14: 2657-64.
- Bouchet, C. A. and A. Cazauveilh (1826). Recherches sur la nature et la sieze de ces deux maladies. *Archives Generales de Medicine*, 1826; 10: 5.
- Breckwoldt, M., P. Wieacker and F. Geisthövel F (1990). Oral contraception in disease states. *Am J Obstet Gynecol*, 163(6 Pt 2):2213-2216.
- Buffel, I., A. Meurs, J. Portelli, R. Raedt, V. De Herdt, L. Sioncke, W. Wadman, F. Bihel, M. Schmitt, K. Vonck, J.I. Bourguignon, F. Simonin, I. Smolders and P. Boon (2015). Neuropeptide FF and prolactin-releasing peptide decrease cortical excitability through activation of NPPF receptors. *Epilepsia*, 56(3):489-98.
- Buntner, B. and D. Rosciszewska (1975). Urinary excretion of estrogen fractions, alpha and beta pregnanediol and pregnanetriol in women with epileptic seizures during the premenstrual period. *Neurol Neurochir Pol.*, 9(3): 311-317.
- Burneo, J.G., J. Tellez-Zenteno and S. Wiebe (2005). Understanding the burden of epilepsy in Latin America: a systematic review of its prevalence and incidence. *Epilepsy Res.*, 66(1-3): 63-74.
- Canter, A., C.Y. Kondo and J.R. Knott (1975). A comparison of EMG feedback and progressive muscle relaxation training in anxiety neurosis. *Br J Psychiatry*, 127:470-477.
- Cardarelli, W.J. and B.J. Smith (2010). The burden of epilepsy to patients and payers. *Am J Manag Care*, 16(12 Suppl):S331-336.
- Castilla-Guerra, L., M. del Carmen Fernández-Moreno, J.M. López-Chozas and R. Fernández-Bolaños (2006). Electrolytes disturbances and seizures. *Epilepsia*, 47(12):1990-1998.
- Chai, Z., C. Ma and X. Jin (2019). Homeostatic activity regulation as a mechanism underlying the effect of brain stimulation. *Bioelectron Med.*, 5:16. doi: 10.1186/s42234-019-0032-0.
- Chalissery, A. J., E. Murphy, G. Mullins, P. Widdess-Walsh, R. Kilbride and N. Delanty (2017). Recurrent catamenial status epilepticus: Is it rare or an under recognized phenomenon in women with epilepsy? *Epilepsy Behav Case Rep.*, 9:19-21.
- Crawford, P. (2005). Best practice guidelines for the management of women with epilepsy. *Epilepsia*, 46 (Suppl 9):117-124.
- Delgado-Escueta, A.V., A.A. Ward, D.M. Woodbury and R.J. Porter (1986). *Basic mechanisms of the epilepsies*, 1986; Raven Press, New York
- Demirkhanyan, L., V. Krishnan, S. Asuthkar, B. Alexander, Z. Hussain, P. Baskaran, Y. Nersesyan, A. Cohen, E. Pavlov, B. Thyagarajan and E. Zakharian (2018). TRPM8 regulates sexual desire and satiety. *Biophysical Journal*, 114 (3), Supplement 1, p643a.
- Driefuss, F.E. (1987). The different types of epileptic seizures and the international classification of epileptic seizures and of the epilepsies. In: *Epilepsy* (Ed. Hopkins A, Chapman and Hall, London, p. 98.
- Duncan, S., C.L. Read and M.J. Brodie (1993). How common is catamenial epilepsy? *Epilepsia*, 34(5):827-31.
- Dwyer, B.E., C.G. Wasterlain, D.G. Fujikawa and L. Yamada (1986). Brain protein metabolism in epilepsy. *Adv Neurol.*, 44:903-918.

- Echodu, R., H. Edema, G.M. Malinga, A. Hendy, R. Colebunders, J. Moriku Kaducu, E. Ovuga and G. Haesaert (2018). Is nodding syndrome in northern Uganda linked to consumption of mycotoxin contaminated food grains? *BMC Res Notes*, 11(1):678.
- Eh Suk VR, A. Marlina, Z. Hussain and M. Misran (2021). N-Stearoyl Chitosan as a Coating Material for Liposomes Encapsulating Itraconazole. *Arabian Journal for Science and Engineering*, 46 (6): 5645-5653.
- Eid, A., C. Kallik, R. Aly, Y.H. Li, N. Taweh and A. Sheth (2025). Seizure Cycle app: A feasibility study. *Epilepsy Behav.*, 164:110305. doi: 10.1016/j.yebeh.2025.110305.
- El-Khayat, H.A., N.A. Soliman, H.Y. Tomoum, M.A. Omran, A.S. El-Wakad and R.H. Shatla (2008). Reproductive hormonal changes and catamenial pattern in adolescent females with epilepsy. *Epilepsia*, 49:1619-1626.
- Engel, J. Jr. (2006) Report of the classification core group. *Epilepsia*, 47:1558-1568.
- Fatima, S., N.I. Khan, G. Yasmeen, B. Hajir and Z. Hussain (2007). Antiatherogenic effects of Nigella Sativa (Kalonji) in rabbits with experimentally induced hypercholesterolemia. *Int J Biol Biotech.*, 4(4):437-441.
- Foldvary-Schaefer, N. and T. Falcone (2003). Catamenial epilepsy: pathophysiology, diagnosis, and management. *Neurology*, 61(6 Suppl 2): S2-15.
- Forsgren, L., E. Beghi, A. Oun and M. Sillanpaa (2005). The epidemiology of epilepsy in Europe: a systematic review. *Eur J Neurol*, 12:245-253.
- Frank, S. and N.A. Tyson (2020). A Clinical Approach to Catamenial Epilepsy: A Review. *Perm J.*, 24:1-3.
- Fujita, Y., Y. Imai, W. Ishii, A. Endo, C. Arakawa, R. Kohira, T. Fuchigami, O. Okubo and H. Mugishima (2011). Improvement of intractable childhood epilepsy following acute viral infection. *Brain Dev.*, 33(1):62-8.
- Gastaut, H. (1973). *Dictionary of epilepsy*, Part I: Definitions, WHO, Geneva.
- Gibbs, F.A., E.L. Gibbs and W.G. Lennox (1937). Epilepsy: A paroxysmal cerebral dysrhythmia. *Brain*, 60 (4): 377-388.
- Giblin, K.A. and H. Blumenfeld (2010). Is epilepsy a preventable disorder? New evidence from animal models. *Neuroscientist*, 16(3):253-275.
- Gilad, R., M. Sadeh, A. Rapoport, R. Dabby and Y. Lampl (2008). Lamotrigine and catamenial epilepsy. *Seizure*, 17(6):531-534.
- Glaser, G.H. and L.L. Levy (1990). Seizures and idiopathic hypoparathyroidism, *Epilepsia* (Amsterdam), 1: 454-465.
- Gloor, P. (1990). Experiential phenomena of temporal lobe epilepsy. Facts and hypotheses. *Brain*, 113(Pt 6):1673-1694.
- Goddard, G.V. (1967). Development of epileptic seizures through brain stimulation at low intensity. *Nature*, 214(5092):1020.
- Grover, S., M. Gourie-Devi, K. Bala, S. Sharma and R. Kukreti (2012). Genetic association analysis of transporters identifies ABCC2 loci for seizure control in women with epilepsy on first-line antiepileptic drugs. *Pharmacogenet Genomics*, 22(6):447-465.
- Grudzinska, B. and D. Rosciszewska (1980). Dynamics of EEG changes during the menstrual cycle in epileptic women. In: *Abstracts of XI Meeting of the Polish Neurological Association*. Bydgoszcz, P. 61.
- Haglund, M.M. and P.A. Schwartzkroin (1990). Role of Na-K pump potassium regulation and IPSPs in seizures and spreading depression in immature rabbit hippocampal slices. *J Neurophysiol*, 63(2): 225-239.
- Hamed, S.A., M.M. Abdellah and N. El-Melegy (2004). Blood levels of trace elements, electrolytes, and oxidative stress/antioxidant systems in epileptic patients. *J Pharmacol Sci.*, 96(4):465.
- Hansen, S.L., A.H. Nielsen, K.E. Knudsen, A. Artmann, G. Petersen, U. Kristiansen, S.H. Hansen and H.S. Hansen (2009). Ketogenic diet is antiepileptogenic in pentylenetetrazole kindled mice and decrease levels of N-acylethanolamines in hippocampus. *Neurochem Int.*, 54(3-4):199-204.
- Harden, C.L. (2008). Issues for mature women with epilepsy. *Int Rev Neurobiol.*, 83:385-95.
- Harden, C.L. and I. Leppik (2006). Optimizing therapy of seizures in women who use oral contraceptives. *Neurology*, 67(Suppl 4):S56-58.
- Helmchen, H., H. Kunkel and H. Selbach (1964). Periodic influences on the individual frequency of epileptic seizures. *Arch Psychiatr Nervenkr*, 206 :293-308.
- Herzog, A.G. (1988). Clomiphene therapy in epileptic women with menstrual disorders. *Neurology*, 38(3):432-4.
- Herzog, A.G. (2015). Catamenial epilepsy: current concepts of definition, prevalence, pathophysiology and treatment. *Zeitschrift fur Epileptol*, 2015; 28: 295-303.
- Herzog, A. G. and C.A. Frye (2014). Progesterone Trial Study Group. Allopregnanolone levels and seizure frequency in progesterone-treated women with epilepsy. *Neurology*, 83(4):345-8.

- Herzog, A.G., K.M. Fowler, S.D. Smithson, L.A. Kalayjian, C.N. Heck, M.R. Sperling, J.D. Liporace, C.L. Harden, B.A. Dworetzky, P.B. Pennell and J.M. Massaro (2012). Progesterone Trial Study Group. Progesterone vs placebo therapy for women with epilepsy: A randomized clinical trial. *Neurology*, 78(24):1959-1966.
- Herzog, A.G. and K.M. Fowler (2008). NIH Progesterone Trial Study Group. Sensitivity and specificity of the association between catamenial seizure patterns and ovulation. *Neurology*, 70(6):486-487.
- Herzog, A.G., P. Klein and B.J. Ransil (1997). Three patterns of catamenial epilepsy. *Epilepsia*, 38(10):1082-8.
- Herzog, A.G., C.L. Harden, J. Liporace, P. Pennell, D.L. Schomer, M. Sperling, K. Fowler, B. Nikolov, S. Shuman and M. Newman (2004). Frequency of catamenial seizure exacerbation in women with localization-related epilepsy. *Ann Neurol.*, 56(3):431-434.
- Herzog, A.G. (2006). Menstrual disorders in women with epilepsy. *Neurology*, 66(6 Suppl 3):S23-28.
- Herzog, A.G. (2008). Catamenial epilepsy: definition, prevalence pathophysiology and treatment. *Seizure*, 17(2):151-59.
- Hill, D. (1958). Value of the EEG in diagnosis of epilepsy, *Brit Med J.*, 1(5072): 663-666.
- Hoffman, W.H. and L.B. Haberly (1993). Role of synaptic excitation in the generation of bursting-induced epileptiform potentials in the endopiriform nucleus and piriform cortex. *J Neurophysiol.*, 70(6):2550-2561.
- Hojo, Y., S. Higo, H. Ishii, Y. Ooishi, H. Mukai, G. Murakami, T. Kominami, T. Kimoto, S. Honma, D. Poirier and S. Kawato (2009). Comparison between hippocampus-synthesized and circulation-derived sex steroids in the hippocampus. *Endocrinology*, 150(11): 5106-5112.
- Holmes, G.L. and D.A. Weber (1984). The effect of progesterone on kindling: a developmental study. *Brain Res.*, 318(1):45-53.
- Hom, A.C. and G.G. Buterbaugh (1986). Estrogen alters the acquisition of seizures kindled by repeated amygdala stimulation or pentylene-tetrazole administration to ovariectomized female rats. *Epilepsia*, 27(2):103-108.
- Hopkins, A. (1987). *Epilepsy*. Chapman and Hall. London, p. 1.
- Hussain, M.H. and Z. Hussain (2020). Common cold in children-diagnostic considerations *International Journal of Biology and Biotechnology*, 17 (3): 455-458.
- Hussain, Z. (2024 b). Investigating the role of serum hepcidin and interleukin-6 in non-anemic women with acute ischemic stroke. *International Journal of Biomedicine*, 14(2): 260-264.
- Hussain, Z. (2024 a). Sodium channel hydrogen bonding in epilepsy: molecular physiology and biophysics. *International Journal of Biology and Biotechnology*, 21 (1): 45-52
- Hussain, Z. (2022 b). Serum C-reactive protein as inflammatory marker in men with epilepsy *Int J Biol Biotech.*, 19 (4): 605-610.
- Hussain, Z. (2022 a). Electrophysiology of membrane potentials: mathematical physiology and mathematical medicine perspectives. *Int. J. Biol. Biotech.*, 19 (2): 161-170
- Hussain, Z., L. Demirkhanyan, S. Asuthkar and E. Zakharian (2017). Testosterone is a Highly Potent and Specific Agonist of TRPM8. *Biophysical Journal*, 110 (3), Supplement 1, p613a.
- Hussain, Z. (2010). *Menstrual Cycle and Epilepsy: Premenstrual Reproductive Study*. Germany (Printed in USA & UK). German National Library-Thomson Reuters-ISI Copyright Library. Pages:239.
- Hussain, Z., K.Z. Hasan, H. Aziz and M.A. Qureshi (2007a). Clinical and neurological study of women with precatamenial epilepsy. *J Coll Physicians Surg Pak.*, 17(4):211-214.
- Hussain, Z., S. Sohail and A. Ashraf (2007b). Blood cholesterol concentration in smoking and non-smoking patients with diabetes mellitus. *Hum Health*, 3 (7&8): 5-8.
- Hussain, Z., M.A. Qureshi, K.Z. Hasan and H. Aziz (2006). Influence of steroid hormones in women with mild catamenial epilepsy. *Journal of Ayub Medical College Abbottabad*, 18(3):17-20.
- Hussain, Z. (2001). Modified progressive relaxation- Psychophysiological foundations of medicine. *The Med Intern.*, 4: 5-7.
- Hussain, Z. (1994). Modified progressive relaxation therapy-discovery of a new horizon in psychobiology. *Med Rev.*, 6 (1): 3-5.
- Hussain, Z. (1991). *Clinical, electroencephalographic and hormonal study in menstruation related seizures* (Ph.D. thesis), Department of Physiology, University of Karachi, with the Faculty of Medicine, Department of Neuropsychiatry, Epilepsy Clinic & EEG (Electroencephalography) Lab, JPMC, Karachi.
- Hussain, Z. (Azeemi, Z.H.), M.A. Qureshi, K.Z. Hasan and H. Aziz (1987). Effect of anticonvulsants on seizure occurrence in women with epilepsy. *Annals of JPMC*, 4 (1): 13-18
- Hussain, Z. (1984). *Steroids, neurosteroids, PMS, catamenial epilepsy and MPR therapy*. Monograph, Dept of Neuropsychiatry, JPMC, Karachi.
- Hussain, Z. (1983). *Effect of stimulation frequency on fatigue occurrence in skeletal muscles* (M.Sc. thesis), Department of Physiology, University of Karachi.

- Hussain, Z. (1982). *MPR therapy and Jacobson's progressive relaxation therapy*. Monograph, Dept of Neuropsychiatry, JPMC, Karachi.
- Hussain, Z. and K.Z. Hassan (1982). *Anemia of inflammation and autoimmune anemia*. Monograph. Department of Neuro-Psychiatry, Faculty of Medicine, Jinnah Postgraduate Medical Centre (JPMC), Karachi.
- Inam, S., S. Masood, K. Abbas, N. Khan and Z. Hussain (1995). Changes in plasma calcium under influence of estradiol valerate. *First National Conference on Pharmacology and Therapeutics*. Faculty of Pharmacy, University of Karachi. P: 45.
- Inam, S., S. Masood, M.A. Siddiqui and Z. Hussain (1994). *Skin infections caused by virus*. Biological Foundations of Medicine, p: 11-12.
- International Classification of Functioning and Disability (1999). *Beta-2 Draft, Full Version*. Geneva. World Health Organization,
- Isojarvi, J.I. (1990). Serum steroid hormones and pituitary function in female epileptic patients during carbamazepine therapy. *Epilepsia*, 31(4):438-445.
- Isojarvi, J.I., E. Taubøll and A.G. Herzog (2005). Effect of antiepileptic drugs on reproductive endocrine function in individuals with epilepsy. *CNS Drugs*, 19(3):207-223.
- Jacobson, E. (1938). *Progressive relaxation*. Chicago: University of Chicago Press.
- Jacobson, E. (1929). *Progressive relaxation*. Chicago: University of Chicago Press.
- Jacobson E. (1927). Action currents from muscular contractions during conscious processes. *Science*, 66(1713):403.
- Jacono, J.J. and J.M. Robertson (1987). The effects of estrogen, progesterone, and ionized calcium on seizures during the menstrual cycle of epileptic women. *Epilepsia*, 28: 571-577.
- Jallon, P. and F. Picard (2001). Bodyweight gain and anticonvulsants: a comparative review. *Drug Saf.*, 24(13):969-978.
- Jallon, P., P. Louiset and P. Loiseau (1986). Epileptics, beware of colds! Danger of drugs containing phenylpropanolamine. *Presse Med.*, 15(37):1877-78.
- Joshi, S. and J. Kapur (2019). Neurosteroid regulation of GABA<sub>A</sub> receptors: A role in catamenial epilepsy. *Brain Res.*, 1703:31-40.
- Joshi, S., H. Sun, K. Rajasekaran, J. Williamson, E. Perez-Reyes and J. Kapur (2018). A novel therapeutic approach for treatment of catamenial epilepsy. *Neurobiol Dis.*, 111:127-137.
- Kansal, B., A. Anand, D. Garg, A. Gupta, A. Kumar and S. Sharma (2022). Applicability of the International League Against Epilepsy (ILAE) 2022 diagnostic criteria for epilepsy syndromes in children: A retrospective review of 1550 children with epilepsy. *Seizure*, 117:288-292.
- Kapur, J. and S. Joshi (2021). Progesterone modulates neuronal excitability bidirectionally. *Neurosci Lett.*, 744:135619.
- Kariyawasam, S.H., U. Mannapperuma, W.J. Jayasuriya, J. Weerathunga and K. Munasinghe (2009). Occurrence of menstrual cycle related seizure patterns among epileptic women attending the tertiary neurology clinics of the National Hospital of Sri Lanka. *Epilepsy Res.*, 84: 257-62.
- Khan, N.I., L. Naz, S. Mushtaq, L. Rukh, S. Ali and Z. Hussain (2009). Ischemic stroke: prevalence of modifiable risk factors in male and female patients in Pakistan. *Pak J Pharm Sci.*, 22(1):62-67.
- Khan, N.I. and Z. Hussain (2008). Pathophysiology of ischemic disorders: 1- LDL cholesterol and Ischemic stroke. *Int J Biol Biotech.*, 5 (1-2):1-16.
- Khan, N., K. Abbas, S. Masood, S. Inam and Z. Hussain (1995). Effect of estradiol valerate on plasma cholesterol in Uromastix hardwickii. *First National Conference on Pharmacology and Therapeutics*. Faculty of Pharmacy, University of Karachi. P: 43.
- Khoiny, F.E. (1996) Use of depo-provera in teens. *J Pediatr Health Care*, 10(5):195-201.
- Kiloh, L.G., A. J. McComas, J.W. Osselton, and A.R.M. Upton (1981). *Clinical electroencephalography*. 1981; Butterworth and Company, London, p. 88.
- Kramer, M.S. (1977). Menstrual epileptoid psychosis in an adolescent girl. *Am J Dis Child.*, 131(3):316-17.
- Kuba, R., M. Pohanka, J. Zákopčan, I. Novotná and I. Rektor (2006). Sexual dysfunctions and blood hormonal profile in men with focal epilepsy. *Epilepsia*, 47(12):2135-2140
- Kumar, N., M. Behari, G.K. Ahuja and B.L. Jaikhani (1988). Phenytoin levels in catamenial epilepsy. *Epilepsia*, 29(2):155-158.
- Laidlaw, J. (1956). Catamenial epilepsy, *Lancet*, 271(6955):1235-1237.
- Laidlaw, J. and A. Richens (1982). *A textbook of epilepsy*. Churchill Livingstone, Edinburgh.
- Lemley, R.J. and P.E. Voinescu (2023). Assisted reproductive technology outcomes and management considerations for people with epilepsy. *Curr Opin Endocrinol Diabetes Obes*, 30(6):280-284.
- Lennox, W.G. (1955). The rign of the uterus, *Epilepsia*, 4:91-98.

- Leppik, I.E. and A.K. Birnbaum (2010). Epilepsy in the elderly. *Ann N Y Acad Sci.*, 1184:208-24.
- Li, Q., X.Q. Dai, P.Y. Shen, Y. Wu, W. Long, C.X. Chen, Z. Hussain, S. Wang and X.Z. Chen (2007). Direct binding of alpha-actinin enhances TRPP3 channel activity. *J Neurochem.*, 103(6):2391-400.
- Liang, S., J. Zhao, W. Zhao, N. Jia, Z. Zhang, B. Li (2024). Qualitative and Quantitative Detection of Typical Reproductive Hormones in Dairy Cows Based on Terahertz Spectroscopy and Metamaterial Technology. *Molecules*, 29(10):2366.
- Lim, L.L, N. Foldvary, E. Mascha and J. Lee (2001). Acetazolamide in women with catamenial epilepsy. *Epilepsia*, 42(6):746-9.
- Liu, X. and J. Chen (2022). Research progress on ferroptosis and its role in epilepsy. *J Physiol Pharmacol.*, 73(6). doi: 10.26402/jpp.2022.6.02.
- Livingston, S. (1972). *Comprehensive management of epilepsy in infancy, childhood and adolescence*. CC Thomas, Springfield, Ill.
- Logothetis, J., R. Haner, F. Morrell and F. Torres (1959). The role of estrogen in catamenial exacerbation of epilepsy. *Neurology*, 9: 352-360.
- Luef, G.(2010). Hormonal alterations following seizures. *Epilepsy Behav.*, 19(2):131-3.
- Maguire, M.J. and S.J. Nevitt (2021). Treatments for seizures in catamenial (menstrual-related) epilepsy. *Cochrane Database Syst Rev.*, 9(9):CD013225.
- Mahmood, A. and Z. Hussain (1999). Common colds- prevention and general measures. *The Medicine International*, 2 (2), 7-9.
- Mahmood, A. and Z. Hussain (1998). Clinical and epidemiological aspects of common colds. *The Medicine International*, 1 (5), 3-5
- Marek, B., D. Kajdaniuk, B. Kos-Kudła, J. Kapustecki, E. Swietochowska, Z. Ostrowska, L. Siemińska, M. Nowak, J. Głogowska-Szelag, H. Borgiel-Marek, N. Ciesielska-Kopacz, W. Foltyn, K. Pierzchała, R. Krysiak and R. Bienek (2010). Mean daily plasma concentrations of beta-endorphin, leu-enkephalin, ACTH, cortisol, and DHEAS in epileptic patients with complex partial seizures evolving to generalized tonic-clonic seizures. *Endokrynol Pol.*, 61(1):103-110.
- Marsden, C.D and E.H. Reynolds (1982). Neurology-Part I In: *A Textbook of Epilepsy*, (Ed. Laidlaw J and Richens A), Churchill Livingstone, New York, P. 97.
- Masood, S., S. Inam, K. Abbas, N. Khan and Z. Hussain (1995). Fluctuation in plasma sodium in response to estradiol valerate *First National Conference on Pharmacology and Therapeutics*. Faculty of Pharmacy, University of Karachi. P: 46.
- Matias, C., M.H. Hussain and Z. Hussain (2017). Lipid membrane-estrogen interaction: molecular and biophysical perspective: A mini overview. *International Journal of Biology Research*, 5 (2): 35-42.
- Matsubara, Y., S. Akamine, P.F. Chong, S. Kawakami, K. Maehara, Y. Kaku, M. Kurokawa, N. Morisada, K. Iijima and R. Kira (2021). Infantile spasms and early-onset progressive polycystic renal lesions associated with TSC2/PKD1 contiguous gene deletion syndrome. *Seizure*, 86:82-84.
- McKee, H.R. and M.D. Privitera (2017). Stress as a seizure precipitant: Identification, associated factors, and treatment options. *Seizure*, 44:21-26.
- McQuarrie, I. (1932). Some recent observations regarding the nature of epilepsy. *Ann Intern Med.*, 6(4) :497-505.
- Meisler, M.H. and J.A. Kearney (2005). Sodium channel mutations in epilepsy and other neurological disorders. *J Clin Invest.*, 115(8):2010-2017.
- Merlis, J.K. (1972). Treatment in relation to classification of the epilepsies. *Acta Neurologica Latinoamericana*, 18(1):42-51.
- Mohandass, A., V. Krishnan, E.D. Gribkova, S. Asuthkar, P. Baskaran, Y. Nersesyan, Z. Hussain, L.M. Wise, R.E. George, N. Stokes, B.M. Alexander, A.M. Cohen, E.V. Pavlov, D.A. Llano, M.X. Zhu, B. Thyagarajan and E. Zakharian (2020). TRPM8 as the rapid testosterone signaling receptor: Implications in the regulation of dimorphic sexual and social behaviors. *FASEB J.*, 34(8):10887-10906.
- Morrell, M.J. (1999). Epilepsy in women: the science of why it is special. *Neurology*, 53(4 Suppl 1): S42-48.
- Morrell, M.J., J. Isojärvi, A.E. Taylor, M. Dam, R. Ayala, G. Gomez, F. O'Neill, P. Tennis and J. Messenheimer (2003). Higher androgens and weight gain with valproate compared with lamotrigine for epilepsy. *Epilepsy Res.*, 54(2-3):189-199.
- Morrell, M.J. and G.D. Montouris (2004). Reproductive disturbances in patients with epilepsy. *Cleve Clin J Med.*, 71(Suppl 2):S19-24.
- Motta, E., A. Golba, Z. Ostrowska, A. Steposz, M. Huc, J. Kotas-Rusnak, J.J. Łuszczki, S.J. Czuczwar and W. Lasoń (2013). Progesterone therapy in women with epilepsy. *Pharmacol Rep.*, 65(1):89-98.
- Munir, R and Z. Hussain (1999). Epidemiology of common colds. *The Medicine International*, 2 (3), 3-5

- Mumtaz, A., A. Khalid, Z. Hussain, F. Alam and R. Rehman R (2016). Kisspeptin and unexplained infertility. 2nd Annual conference of Ziauddin University & European Society of Translational Medicine.
- Navis, A. and C. Harden (2016). A Treatment Approach to Catamenial Epilepsy. *Curr Treat Options Neurol.*, 18(7):30.
- Naz, L., Z. Hussain and T. Husain (2009). Risk factors and biochemical variations in patients with ischemic stroke. *Int J Biol Biotech.*, 6 (1-2):83-87.
- Neshige, S., S. Aoki, T. Nezu, M. Nakamori, Y. Yamazaki, T. Ohshita and H. Maruyama (2023). Are patients with Parkinson's disease at a lower risk of catching the common cold? Propensity score matching. *Parkinsonism Relat Disord.*, 106:105227.
- Newmark, M.E. and J.K. Penry (1980). Catamenial epilepsy: A review. *Epilepsia*, 21: 281-300.
- Ngugi, A.K., C. Bottomley, I. Kleinschmidt, J.W. Sander and C.R. Newton (2010). Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia*, 51(5):883-90.
- Niu, R., X. Guo, J. Wang and X. Yang (2025). The hidden rhythms of epilepsy: exploring biological clocks and epileptic seizure dynamics. *Acta Epileptol.*, 7(1):1. doi: 10.1186/s42494-024-00197-w.
- Octaviana, F., K. Sumapraja, W. Wiratman, L.A. Indrawati and A. Budikayanti (2022). Characteristics of menstrual disorders and reproductive hormones in women with epilepsy at an Indonesian national referral hospital. *Front Neurol*, 13:964761.
- Ogihara, M, S. Shirakawa, T. Miyajima, K. Takekuma and A. Hoshika (2010). Diurnal variation in febrile convulsions. *Pediatr Neurol.*, 42(6):409-412.
- Parekh, K., H.D. Kravets and R. Spiegel (2022). Special Considerations in the Management of Women with Epilepsy in Reproductive Years. *J Pers Med.*, 12(1):88. doi: 10.3390/jpm12010088.
- Patel, S.I. and N. Foldvary-Schaefer (2014). Catamenial epilepsy. In: Bui B, Klein A. *Women with epilepsy: a practical management handbook*. Cambridge: Cambridge University Press; p. 101-112.
- Penfield, W. and T.C. Erickson (1941). *Epilepsy and cerebral localization*. Bailliere, Tindal and Cox, London, p. 12
- Penfield, W. and H. Jasper (1954). *Epilepsy and the functional anatomy of the human brain*. Little Brown, Boston
- Pennell, P.B. (2009). Hormonal aspects of epilepsy. *Neurol Clin.*, 2009; 27(4):941-965.
- Pitkänen, A., I. Kharatishvili, H. Karhunen, K. Lukasiuk, R. Immonen, J. Nairismägi, O. Gröhn and J. Nissinen (2007). Epileptogenesis in experimental models. *Epilepsia*, 48 Suppl 2:13-20.
- Polack, P.O., I. Guillemain, E. Hu, C. Deransart, A. Depaulis and S. Charpier (2007). Deep layer somatosensory cortical neurons initiate spike- and-wave discharges in a genetic model of absence seizures. *J Neurosci.*, 27:6590-6599.
- Porter, R.J. (1984). *Epilepsy: 100 elementary principles*. WB Saunders Company, London. p. 14
- Prabhakar, S., P. Sahota, P.S. Kharbanda, R. Siali, V. Jain, V. Lal and D. Khurana (2007). Sodium valproate, hyperandrogenism and altered ovarian function in Indian women with epilepsy: a prospective study. *Epilepsia*, 48(7):1371-1377.
- Presl, J. (1991). Favorable effects of oral estrogen-progestin contraception. *Cesk Gynekol.*, 56(5-6):350-352.
- Qureshi, M.A., Z. Hussain (Z.H. Azeemi), H. Aziz and K.Z., Hasan (1988). Changes in estrogen and progesterone, seizure occurrence and effect of anticonvulsant medication in catamenial epileptics. *FASEB (Fed Amer Soc Exp Biol) J*, 2 (5): 4500.
- Rebar, R.W. and S.S.C. Yen (1979). Endocrine rhythms in gonadotrophins and ovarian steroids with reference to reproductive process. In: *Endocrine Rhythms* (Ed. Krieger, DT), Raven Press, New York, p. 259.
- Reddy, D.S. (2022). Neurosteroid replacement therapy for catamenial epilepsy, postpartum depression and neuroendocrine disorders in women. *J Neuroendocrinol.*, 34(2):e13028.
- Reddy, D.S. (2004). Role of neurosteroids in catamenial epilepsy. *Epilepsy Res.*, 62(2-3):99-118.
- Reddy, D.S., H.Y. Kim and M.A. Rogawski (2001). Neurosteroid withdrawal model of perimenstrual catamenial epilepsy. *Epilepsia*, 42(3):328-36.
- Reddy, D.S. (2009). The role of neurosteroids in the pathophysiology and treatment of catamenial epilepsy. *Epilepsy Res.*, 85(1):1-30.
- Reddy, D.S. (2020). Brain structural and neuroendocrine basis of sex differences in epilepsy. *Handb Clin Neurol.*, 175: 223-233.
- Rehman, R., Z. Hussain, S.S. Fatima, F. Alam and H. Gul (2016). *Impact of obesity on infertility*. Research Day, Department of Medicine, Aga Khan University, Karachi. P: 10.6
- Rehman, R., Z. Hussain, S.S. Fatima, F. Alam and H. Gul (2015). Effect of body mass index on implantation after intracytoplasmic sperm injection. *6th Annual Research Day, Feb 2015, Conference*. (Dow University of Health Sciences) DUHS, Karachi

- Rehman, R., Z. Hussain, H. Zahir and R. Khan (2014). Impact of peak/mid luteal estradiol on pregnancy outcome after intracytoplasmic sperm injection. *J Pak Med Assoc.*, 64(7):780-784.
- Rehman, R., Z. Hussain, S. Jawaid, H. Gul and R. Khan (2013d). *Effect of estradiol on ovarian cycle*. JSMU (Jinnah Sindh Medical University), Karachi.
- Rehman, R., Z. Hussain and S.S. Fatima (2013c). Effect of weight status on pregnancy outcome in intra cytoplasmic sperm injection. *Iran J Reprod Med.*, 11(9):717-724.
- Rehman, R., Z. Hussain and N.A. Zuberi (2013b). Prediction of success in intracytoplasmic sperm injection (ICSI) by estimation of serum estradiol/progesterone ratio on the day of embryo transfer. *J Pak Med Assoc.*, 63(5):609-613.
- Rehman, R., Z. Hussain and N. Faraz (2013 a). Effect of body mass index on reproductive outcome after intra cytoplasmic sperm injection 3rd BUMDC (Bahria University Medical & Dental College) symposium. Karachi.
- Rehman, R., Z. Hussain and A.A. Siddiq (2012a). Role of Progesterone in Human Embryo Implantation. *Rawal Medical Journal*, 37(2):194-198.
- Rehman, R., Z. Hussain and N. Faraz (2012b). Effect of estradiol levels on pregnancy outcome in obese women. *J Ayub Med Coll Abbottabad*, 24(3-4):3-5.
- Reynolds, M.F., E.C. Sisk and N.L. Rasgon (2007). Valproate and neuroendocrine changes in relation to women treated for epilepsy and bipolar disorder: a review. *Curr Med Chem.*, 14(26):2799-2812.
- Rider, F, A. Turchinets, T. Druzhkova, G. Kustov, A. Guekht and N. Gulyaeva (2024). Dissimilar Changes in Serum Cortisol after Epileptic and Psychogenic Non-Epileptic Seizures: A Promising Biomarker in the Differential Diagnosis of Paroxysmal Events? *Int J Mol Sci.*, 25(13):7387.
- Roeder. H.J. and E.C. Leira (2021). Effects of the Menstrual Cycle on Neurological Disorders. *Curr Neurol Neurosci Rep.*, 21(7):34.
- Rosciszewska, D. (1974). *Clinical course of epilepsy during puberty, maturity and climacterium*. Dissertation, Katowice, p.25.
- Rosciszewska, D. (1980). Analysis of seizure dispersion during menstrual cycle in women with epilepsy. *Monog Neural Sci.*, 5: 280-284.
- Rosciszewska, D. (1987). Epilepsy and menstruation. In: *Epilepsy*, (Ed. Hopkins, A.), Chapman and Hall, London, p. 373.
- Rościszewska, D., B. Buntner, I. Guz and L. Zawisza (1986). Ovarian hormones, anticonvulsant drugs, and seizures during the menstrual cycle in women with epilepsy. *J Neurol Neurosurg Psychiatry*, 49(1):47-51.
- Rosciszewska, D., J. Dutkiewicz and A. Blecharz (1985). Luteinizing hormone (LH) serum level during the menstrual cycle in female epileptic patients. *Neurol Neurochirurg Pol.*, 29: 205-210.
- Røste, L.S. and E. Taubøll (2007). Women and epilepsy: review and practical recommendations. *Expert Rev Neurother*, 7(3):289-300.
- Rousseau, A., B. Hermann and S. Whitman (1985). Effects of progressive relaxation on epilepsy: analysis of a series of cases. *Psychol Rep.*, 57(3 Pt 2):1203-1212.
- Saito, N., K. Shimizu, Y. Yoshii, J. Kojima, T. Ishikawa, K. Saito and K. Kuwano (2013). A case of Legionella pneumophila pneumonia accompanied by acute respiratory distress syndrome and epilepsy. *Kansenshogaku Zasshi.*, 87(3):389-392.
- Saly, V. and R.D. Andrew (1993). CA3 neuron excitation and epileptiform discharge are sensitive to osmolality. *J Neurophysiol.*, 69(6):2200
- Sanchez Longo, L.P. and L.E. Gonzalez Saldana (1966). Hormones and their influence in epilepsy. *Acta Neurol Lat Am.*, 12(1):29-47.
- Sazgar, M., L. Mnatsakanyan, A.M. Pack and C.L. Harden (2023). Epilepsy and Anti-Seizure Medications: Secret Agents for Endocrine Disruption. *Epilepsy Curr.*, 24(2):79-83.
- Sbai, O., R. Soussi, A. Bole, M. Khrestchatsky, M. Esclapez and L. Ferhat (2020). The actin binding protein  $\alpha$ -actinin-2 expression is associated with dendritic spine plasticity and migrating granule cells in the rat dentate gyrus following pilocarpine-induced seizures. *Exp Neurol.*, 335:113512.
- Schachter, S.C. (1988). Hormonal considerations in women with seizures. *Arch Neurol.*, 45(11):1267-1270.
- Schelp, A.O. and J.G. Speciali (1983). Clinical study of catamenial epilepsy: clinical types of epileptic crises. *Arq Neuropsiquiatr*, 41(2):152-157.
- Shah, Q.A., A.A. Jamil, V.P. Gupta, M.M. Kabiraj and A.H. Shah (2001)). Changes in serum electrolytes in childhood epilepsy: A hospital based prospective. *Greenwich J Sci Technol.*, 2:18.
- Shawki, M., L. El Wakeel, R. Shatla, G. El-Saeed, S. Ibrahim and O. Badary (2013). The clinical outcome of adjuvant therapy with black seed oil on intractable paediatric seizures: a pilot study. *Epileptic Disord.*, 15(3):295-301.

- Shiono, S., H. Sun, T. Batabyal, A. Labuz, J. Williamson, J. Kapur and S. Joshi (2021). Limbic progesterone receptor activity enhances neuronal excitability and seizures. *Epilepsia*, 62(8):1946-1959.
- Siddiqui, M.A., S. Inam, S. Masood and Z. Hussain (1994). Etiological factors in hypertension. *Medical Review*, 6 (6): 1-2.
- Singh, H. and D. Pathak (2024). Unveiling the Anti-convulsant Potential of Novel Series of 1,2,4-Triazine- 6H-Indolo[2,3-b]quinoline Derivatives: *In Silico* Molecular Docking, ADMET, DFT, and Molecular Dynamics Exploration. *Curr Comput Aided Drug Des.*, 2024;20(6):822-834.
- Smejkalova, T. and C.S. Woolley (2010). Estradiol acutely potentiates hippocampal excitatory synaptic transmission through a presynaptic mechanism. *J Neurosci.*, 30(48):16137-16148.
- Smith, S.S., H. Shen, Q.H. Gong and X. Zhou (2007). Neurosteroid regulation of GABA(A) receptors: Focus on the alpha4 and delta subunits. *Pharmacol Ther.*, 116(1):58-76.
- Sohail, S., A. Javaid, T.A. Khan, H. Zahir and Z. Hussain (2019) Diabetes mellitus, obesity and adipocytokines pathophysiological perspectives *Int J Biol Biotechnol.*, 16 (2), 325-339.
- Sohail, S. and Z. Hussain (2013). Pathophysiology of ischemic disorders- Ischemia, adipocytokines and diabetes mellitus. *Int J Biol Biotech.*, 10 (2): 155-166.
- Sohail, S., Z. Hussain, Quratul ain, S.J. Ashraf (2013). Blood cholesterol and leptin levels in male smoking and non-smoking patients with diabetes mellitus. *International Journal of Biology Research*, 1(1): 15-18.
- Sohail, S. and Z. Hussain (2009). Influence of diet and physical activity in pre-diabetes. *46th Annual Symposium. JPMC, Karachi, Pakistan*
- Sohail, S. and Z. Hussain (2008). Electrolyte and cholesterol variations in patients with diabetes mellitus. *35th All Pak Sc Conf, Genomics for Health and Prosperity*. University of Karachi, Karachi, Pakistan.
- Stieqlitz, E.J. and S.T. Kimble (1949). Premenstrual intoxication. *Am J M Sc.*, 218: 616-623.
- Stoffel-Wagner, B. (2001). Neurosteroid metabolism in the human brain. *Eur J Endocrinol.*, 145(6):669-679.
- Swann, J.W. and J.J. Hablitz, (2000). Cellular abnormalities and synaptic plasticity in seizure disorders of the immature nervous system. *Ment Retard Dev Disabil Res Rev.*, 6:258-267.
- Takahashi ,T., S. Kamei, K. Miki, K. Ogawa and T. Mizutani (2003). The analysis of cytokines in cerebrospinal fluid (CSF) in two cases of non-herpetic acute limbic encephalitis (NHALE). *Rinsho Shinkeigaku*, 43(4):162-69.
- Taubøll, E., A. Lundervold and L. Gjerstad (1991). Temporal distribution of seizures in epilepsy. *Epilepsy Res.*, 8(2):153-165.
- Taubøll, E., J.I.T. Isojärvi and A.G. Herzog (2021). The interactions between reproductive hormones and epilepsy. *Handb Clin Neurol.*, 182:155-174.
- Taylor, J. (1931). *Selected writings of John Hughlings Jackson*, Vol. 1: On Epilepsy and Epileptiform convulsions, Hodder and Stoughton, London.
- Temkin, O. (1971). *The falling sickness*. The John Hopkins Press, Baltimore, p. 467.
- Thirty, A., C. Heusgem and P. Legentil (1954). Study of the urinary excretion of estrogens, 17 Ketosteroids and reducing steroids in epilepsy, particularly the so called catamenial epilepsy. *Rev Med Liege*, 9.238-246.
- Tuveri A, Paoletti AM, Orrù M, Melis GB, Marotto MF, Zedda P, Marrosu F, Sogliano C, Marra C, Biggio G, Concas A. Reduced serum level of THDOC, an anticonvulsant steroid, in women with perimenstrual catamenial epilepsy. *Epilepsia*. 2008 Jul;49(7):1221-9. doi: 10.1111/j.1528-1167.2008.01555.x. PMID: 18325018.
- Tuveri, A., A.M. Paoletti, M. Orrù, G.B. Melis, M.F. Marotto, P. Zedda, F. Marrosu, C. Sogliano, C. Marra, G. Biggio and A. Concas (2008). Reduced serum level of THDOC, an anticonvulsant steroid, in women with perimenstrual catamenial epilepsy. *Epilepsia*, 49:1221-1229.
- Velíšek, L. and J. Velísková (2008). New avenue of research: antiepileptic drug and estradiol neuroprotection in epilepsy. *Recent Patents CNS Drug Discov*, 3:128-137.
- Velísková, J., G. De Jesus, R. Kaur and L. Velíšek (2010). Females, their estrogens, and seizures. *Epilepsia*, 51 (Suppl 3):141-144.
- Velísková, J. (2007). Estrogens and Epilepsy: Why are we so excited? *Neuroscientist*, 13:77-88.
- Velísková, J. and L. Velíšek (2007). Beta-estradiol increases dentate gyrus inhibition in female rats via augmentation of hilar neuropeptide-Y. *J Neurosci.*, 27:6054-6063.
- Velísková, J., L. Velíšek, A.S. Galanopoulou and E.F. Sperber (2000). Neuroprotective effects of estrogens on hippocampal cells in adult female rats after status epilepticus. *Epilepsia*, 41 Suppl 6:S30-35.
- Voinescu, P.E. and P.B. Pennell (2017). Delivery of a Personalized Treatment Approach to Women with Epilepsy. *Semin Neurol.*, 37(6):611-623.
- Weiner, H.L. and L.P. Levitt (1989). *Neurology for the house officer*, (Ed. Fisher MG.), Williams and Wilkins, Maryland. p. 73.

- W.H.O. (2001a). *Epilepsy: aetiology, epidemiology and prognosis* (Vol. Fact Sheet N 165).
- W.H.O. (2001b). *World Health Organization: epilepsy: epidemiology, aetiology and prognosis*. WHO Factsheet.
- Wilson, S.A.K. (1940). *Neurology*, 2 volumes, Williams and Wilkins, Baltimore.
- Woolley, D.E. and P.S. Timiras (1962a). The gonad-brain relationship: effects of female sex hormones on electroshock convulsions in the rat. *Endocrinology*, 70:196-209.
- Wu, Y.V. and W.M. Burnham (2018). Progesterone, 5 $\alpha$ -dihydroprogesterone and allopregnanolone's effects on seizures: A review of animal and clinical studies. *Seizure*, 63:26-36.
- Wu, Y., X.Q. Dai, Q. Li, C.X. Chen, W. Mai, Z. Hussain, W. Long, N. Montalbetti, G. Li, R. Glynnne, S. Wang, H.F. Cantiello, G. Wu and X.Z. Chen (2006). Kinesin-2 mediates physical and functional interactions between polycystin-2 and fibrocystin. *Hum Mol Genet.*, 15(22):3280-3292.
- Yalçın, A.D., I. Onaran I. and A.S. Yalçın (1994). Effect of antiepileptic drugs on erythrocyte osmotic fragility and lipid peroxidation. *Epilepsy Res.*, 19(3):249-52.
- Yasmeen, G., Z. Hussain and M.L. Bharwani (2009). Gender variations in blood picture of the patients with ischemic acute renal failure. *29th Pakistan Congress of Zoology (International Congress)*, Zoology Society of Pakistan, At: University of Sindh, Jamshoro. P: 150.
- Yasmeen, G., Z. Hussain and M.L. Bharwani (2008). Gender differences in the progression of acute renal failure. *Int J Biol Biotech*, 5 (3-4):215-218.
- Yeung, C.H.T., J.L. Beers, K.D. Jackson and A.N. Edginton (2023). Verifying in vitro-determined enzyme contributions to cannabidiol clearance for exposure predictions in human through physiologically-based pharmacokinetic modeling. *CPT Pharmacometrics Syst Pharmacol*, 12(3):320-332.
- Zafar, F., N. Yasmeen, I. Hussain and Z. Hussain (2001). Effects of ochratoxin incidence in different commercial feeds fed to broilers of Karachi region. *The 21st Pakistan Congress of Zoology*, University of Agriculture, Faisalabad, Zoological Society of Pakistan, Cell Biology, Biochemistry, Genetics and Physiology (CBGP).
- Zafar, F., R. Arshad, Z. Hussain (Z.H. Azeemi) and H.A. Shaikh (1990). A comparative study on the osmotic fragility of erythrocytes in reptile, bird and mammal. *Karachi University Journal of Science*, 18 (1 & 2), 107-117.
- Zaichkina, T.S. (1963). Pathogenesis of so-called menstrual epilepsy. *Zh Nevropatol Psikhiatr.*, 63: 1716-1724.
- Zeidan, M.A., M.A. Alkabbani, S. Giovannuzzi, E.F. Khaleel, A.A. El-Hamaky, N.A. Khattab, R. Badi, A. Abubakr, A.M. Hamdy, M. Fares, H.O. Tawfik, C.T. Supuran, W.M. Eldehna and M.A. Shaldam (2025). Shooting an Arrow against Convulsion: Novel Triazole-Grafted Benzenesulfonamide Derivatives as Carbonic Anhydrase II and VII Inhibitors. *J Med Chem.*, doi: 10.1021/acs.jmedchem.5c00526.
- Zhang, Y., Y. Huang, X. Liu, G. Wang, X. Wang and Y. Wang (2015). Estrogen suppresses epileptiform activity by enhancing Kv4.2-mediated transient outward potassium currents in primary hippocampal neurons. *Int J Mol Med.*, 36(3):865-872.
- Zhang, Z., J. Huang, C. Lin and R. Liang (2025). Identification and validation of LY6H and GRM3 as candidate biomarkers for Glioma-related epilepsy. *Sci Rep.*, 15(1):12833. doi: 10.1038/s41598-025-97333-4.
- Zhao, S. and T. Rohacs. (2021). The newest TRP channelopathy: Gain of function TRPM3 mutations cause epilepsy and intellectual disability. *Channels (Austin)*, 15(1):386-397.
- Zhao, Y., Q. Wang, Z. Ren, B. Wen, Y. Li, N. Wang, B. Wang, T. Zhao, Y. Chen, P. Zhao, M. Li, Z. Zhao, B. Cui, J. Han, Y. Hong and X. Han (2025). A diagnosis and prediction algorithm for juvenile myoclonic epilepsy based on clinical and quantitative EEG features. *Seizure*, 129:59-69.
- Zimmerman, A.W. (1986). Hormones and epilepsy. *Neurol Clin.*, 4(4):853-61.

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