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**Address for Correspondence:**Editorial Room Andalas Obstetrics and Gynecology Journal, 3<sup>rd</sup> floor of KSM of Obstetrics and Gynecology, RSUP DR. M. Djamil Padang, Jl. Perintis Kemerdekaan Padang, Sumatera Barat 25127**Website:**<http://jurnalobgin.fk.unand.ac.id/index.php/JOE>**LITERATURE REVIEW****Premature Ovarian Failure and Epilepsy**Hendra Permana<sup>1</sup>, Afriyeni Sri Rahmi<sup>1</sup>, Syamel Muhammad<sup>2</sup>

*Affiliation author* : 1. Neurology Department, Faculty of Medicine, Andalas University, Dr. M. Djamil Central General Hospital Padang; 2. Sub Division of Oncology Gynecology, Obstetrics and Gynecology Department, Faculty of Medicine, Andalas University, Dr. M. Djamil Central General Hospital Padang

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**Abstract**

Premature ovarian failure (POF) or premature menopause refers to development of amenorrhoea due to cessation of ovarian function before the age of 40 years. The diagnosis is based on elevated FSH levels in menopausal range (usually above 40 IU/l) detected on at least two occasions a few weeks apart. The term “epilepsy” defines a group of disorders characterized by an enduring predisposition of the brain to produce seizures. The hypothalamic-pituitary-ovarian axis regulation is affected by the abnormal neurophysiology of seizures, and the hypothalamic-pituitary-ovarian associated hormones are affected by medications used to treat seizures in women with epilepsy. Ictal and interictal discharges can disrupt the normal activity of brain structures, including the limbic system, amygdala, hypothalamus, and pituitary gland. Management of epilepsy in women requires not only knowledge of epilepsy, but also recognition of the various roles and priorities women have in their lives (education, career development, child rearing, the role as carer within the extended family), and attention to gender-specific issues and their impact on patients’ wellbeing throughout life.

**Keywords:** *premature ovarian failure (POF), epilepsy*

**INTRODUCTION**

Epilepsy is characterized by an enduring predisposition to recurrent seizures. A seizure is an abnormal electrical storm in the brain that causes sudden alterations in consciousness, sensation and behavior that can manifest in forms ranging from an eye flicker to full-body convulsions. Epileptic seizures arise from dysfunctional neuronal network mechanisms that regulate excitability and synchrony.<sup>1</sup>

The issue of sex differences in seizure susceptibility has been long-standing in the study of epilepsy. Clinical evidence shows gender- and age-related expression in many seizure syndromes. The incidence of epilepsy is generally higher in males than in females; however, the prevalence depends a lot on the specific form of epilepsy.<sup>2</sup> More women than men are diagnosed with idiopathic generalized and cyptogenic localization-related epilepsies, but localization-related symptomatic epilepsies are more frequent in men.<sup>2</sup> Furthermore, some findings have shown that in early-onset temporal lobe epilepsy, women show greater functional plasticity for verbal memory than men. The relationship between menstrual cycle and seizure sensitivity in women is well known and is greatly influenced by hormonal fluctuations associated with menstrual cycle phases. However, a recent review yielded no



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consistent evidence of gender differences in the incidence or consequences of these epilepsies.<sup>3</sup> Nevertheless, there is considerable evidence indicating that males exhibit greater seizure susceptibility, while many females exhibit greater fluctuations in susceptibility to seizures, including menstrual cycle-related changes in seizure activity.<sup>3</sup>

Women with epilepsy (WWE) have lower birth rates and fertility rates compared with the general population.<sup>4</sup> Women with treated seizure disorders aged 25–39 years in an unselected population of 2,052,922 people in England and Wales had significantly lower fertility rates than those in the general population. For WWE, there were 47.1 live births per 1000 women aged 15–44 per year (42.3–52.2) compared with a national rate of 62.6 in the same agegroup.<sup>5</sup> The reason for the decrease in fertility in WWE may be related to several reproductive endocrine and psychosocial factors. Individuals with focal epilepsy have higher rates of polycystic ovarian syndrome (PCOS), anovulatory cycles, and premature ovarian failure (POF).<sup>6,7</sup>

**DEFINITION**

Premature ovarian failure (POF) or premature menopause refers to development of amenorrhoea due to cessation of ovarian function before the age of 40 years. The diagnosis is based on elevated FSH levels in menopausal range (usually above 40 IU/l) detected on at least two occasions a few weeks apart.<sup>8</sup>

POF can be considered as an end stage of multiple disorders that ends by loss of ovarian function. However, there are other terms that include POI, when the condition is different because there may be intermittent and unpredictable resumption of the ovarian activity.<sup>9,10</sup>

Insufficient ovarian reserve is usually associated with a disturbance in the FSH, AFC and AMH. However, the cycle is still maintained as normal. Accordingly, there is the possibility of Transitional Ovarian Failure (TOF) which takes 3 to 10 years to develop into POF and is characterised by abnormalities in some ovarian reserve markers mainly FSH elevation >10.2 IU/litre, AFC <5 follicles and AMH <0.5 to 1.1 ng/ml with a regular cycle.<sup>11,12</sup>

The term “epilepsy” defines a group of disorders characterized by an enduring predisposition of the brain to produce seizures. To reduce diagnostic ambiguity and promote a better understanding of the pathogenesis of epilepsy and seizures, the International League Against Epilepsy (ILAE) recently proposed a new definition of epilepsy, which encompasses the following clinical scenarios: i) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; ii) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; iii) an established diagnosis of an epilepsy syndrome.<sup>13</sup>

Focal seizures are further classified as motor/sensory and dyscognitive, whereas generalized seizures encompass tonic-clonic, absence, myoclonic, tonic, clonic or atonic



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seizures.<sup>14</sup> As currently defined, epilepsy is considered to be resolved in patients who have remained seizure-free for at least 10 years and off antiepileptic drugs (AEDs) for at least five years.<sup>15</sup>

## PREVALENCE

Premature ovarian failure (POF) affects approximately 1% of women, occurring in 10–28% of women with primary amenorrhoea and 4–18% in those with secondary amenorrhoea.<sup>16</sup> A wide spectrum of pathogenic mechanisms may lead to the development of POF including chromosomal, genetic, autoimmune, metabolic (galactosaemia), infectious (mumps) and iatrogenic (anticancer treatments) causes. or karyotypically normal spontaneous ovarian failure, whereas up to 30% of cases may have an autoimmune cause.<sup>17,18</sup>

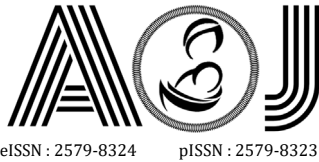
Epilepsy is a relatively common condition, with higher prevalence rates in developing countries. It is estimated that around 3% of people receive a diagnosis of epilepsy at some point in their lifetime, with 70% achieving remission.<sup>19</sup> It is a common neurological condition in women globally, with an estimated prevalence of 6,85 cases per 1000 women.<sup>20</sup> Nearly 1.5 million women of childbearing age in the United States live with epilepsy, and each year approximately 24,000 give birth. Specific challenges arise in caring for women with epilepsy throughout their life cycle from menarche to menopause.<sup>21</sup>

Although sex ratios in the epidemiology of epilepsy are not fully established, there appears to be a slight gender difference in the prevalence of different epilepsy types, such as idiopathic generalized epilepsy and childhood absence epilepsy (2–5 times more common in girls than boys) and juvenile myoclonic epilepsy (1.5 times more common in girls than boys).<sup>22</sup>

The average age of natural menopause in U.S. women is 50.5 years. POF has been defined variably as natural menopause or perimenopause that occurs before age 40–45 years. It affects 1% of women by age 40 years. The incidence of POF in WWE has not been systematically studied. In one previous study, two (4%) of 50 women with TLE had POF, but this group included women aged 20–40 years, and many of them were in their twenties or early thirties, before the age of onset of POF in the general population. In addition, four (8%) women in that series had low serum estradiol levels with-out hypothalamic hypogonadism to indicate declining ovarian function. In another study of menstrual irregularities in women with epilepsy, four of a group of 238 women aged 18–45 years had menopause before age 40 years.<sup>16</sup>

## HOW EPILEPSY INFLUENCE PREMATURE OVARIAN FAILURE

WWE have an increased risk for several reproductive endocrine disorders. About 35% of menstrual cycles of WWE are anovulatory. Women with temporal lobe epilepsy (TLE) have an 20% risk of developing polycystic ovarian syndrome and 15% risk of developing



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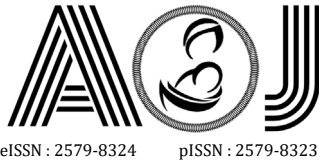
hypothalamic hypogonadism, compared with 5% and 1.5% risk for the two respective conditions in the general population. These conditions may contribute to reduced fertility and birth rate among women with epilepsy, which are 70% of the expected. Premature menopause or perimenopause (premature ovarian failure, (POF) is another reproductive endocrine cause of infertility.<sup>16</sup>

The hypothalamic-pituitary-ovarian axis regulation is affected by the abnormal neurophysiology of seizures, and the hypothalamic-pituitary-ovarian associated hormones are affected by medications used to treat seizures in women with epilepsy. Ictal and interictal discharges can disrupt the normal activity of brain structures, including the limbic system, amygdala, hypothalamus, and pituitary gland.<sup>23</sup> Hepatic enzyme inducing AEDs, specifically cytochrome P450 3A4 (CYP3A4) inducers, affect the metabolism of endogenous sex hormones and thyroid hormones and, therefore, contribute to the dysregulation of the hypothalamic-pituitary-ovarian axis.<sup>24</sup>

At a certain point of time, the majority of primordial follicles in the ovary rest in a quiescent state, avoiding premature follicular depletion, which could end up in POF. Adhikari *et al.* demonstrated the function of tumor suppressor tuberous sclerosis complex 1 (Tsc1) in oocytes to prevent premature activation and therefore maintain the quiescence of primordial follicles, through negative regulation of mammalian target of rapamycin complex 1 (mTORC1) using mutant mouse models. They suggested that Tsc/Mtorc1 signaling pathway and PTEN/PI3K signaling pathway regulate the on-and-off of primordial follicles activation collaboratively, ensuring a normal reproductive lifespan.<sup>25</sup> Meanwhile, novel concept has arisen to challenge traditional understanding of ovarian functions, stating that ovarian germ cells are capable of self-renewal over time. Further studies are required to support such optimistic concept.<sup>26</sup>

Approximately 10% - 15% of POF cases have a positive family history. Many genes have been reported to have association with familial POF.<sup>27</sup> Davis *et al.* looked into 41 cases of familial premature ovarian failure. Clear genetic association has been identified in 11 cases, and the investigation in siblings of the remaining 30 families revealed female sex preponderance, indicating that X chromosome defect is an important cause of familial premature ovarian failure.<sup>28</sup> In 2008, Hunter *et al.* compared women from 225 families with a history of fragile X syndrome with women from families in the general population, and reported significant familial aggregation of age at menopause with an estimated additive genetic variance of 0.55–0.96. Adjustment for *FMR1* repeat size and confounders is performed.<sup>29</sup>

Epilepsy is characterized by three patterns of increased seizure frequency: C1 (perimenstrual pattern: increased frequency of seizures from day 25 of the first cycle to day 3 of the next cycle), C2 (periovulatory pattern: increased seizure frequency on days 10-14) and C3 (luteal pattern: increased frequency of seizures from day 17 of the first cycle to day 3 of



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next cycle when compared with days 4-10, the follicular phase). C1 and C3 are associated with a decrease in progesterone levels, while C2 sees an increase in the level of estrogen.<sup>30</sup> Frequency of generalized tonic-clonic seizures was found to be higher in anovulatory cycles, which were also associated with an increase in the serum estradiol/progesterone ratio.<sup>31</sup>

## ANTIPILEPTIC DRUG EFFECTS

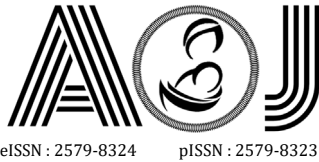
Antiepileptic Drug Effects (AEDs) are known to cause endocrine side effects resulting in abnormalities in fertility, thyroid hormones, sexual function, and bone health. Microsomal hepatic enzyme-inducing AEDs, such as phenytoin, carbamazepine, and phenobarbital, can reduce the circulating bioavailable steroid hormones and, therefore, increase sex hormone-binding globulin concentrations.<sup>32</sup> Valproic acid is also known to cause endocrine side effects. In 1993, Isojärvi conducted the first systematic study of 238 women with epilepsy receiving valproic acid monotherapy. Approximately 45% of these women had menstrual disorders, and of those, 90% had polycystic ovary syndrome or hyperandrogenism, or both.<sup>33</sup>

The risk of developing polycystic ovary syndrome and high testosterone levels was age dependent and highest in women 26 years old and younger. In a prospective study, an increase in serum testosterone and androstenedione levels was seen in half of the women within 3 months of starting valproic acid therapy. The endocrine adverse effects of valproic acid are at least partly reversible. Valproic acid-induced weight gain may exacerbate its endocrine effects. Sexual dysfunction and decreased libido and satisfaction with sex lives are also reported in women taking enzyme-inducing AEDs, such as carbamazepine and phenytoin.<sup>34</sup>

The full endocrine side effect profile of newer AEDs is unknown. Lamotrigine is not found to cause endocrine side effects. In fact, switching from valproic acid to lamotrigine resulted in normalization of endocrine function after a year. Levetiracetam can reduce basal estrogen secretion from ovarian follicles, but it does not affect the gonadotropin-stimulated estrogen secretion.<sup>35</sup> To date, no clinically significant reproductive endocrine side effects have been associated with the use of levetiracetam in women or prepubertal children with epilepsy.<sup>36</sup>

## TREATMENT

Therapeutic strategies to POI are hormone replacement therapy (HRT), infertility rescue, and concern about maintenance of bone health and emotional health as well.<sup>37,38</sup> Long-term HRT is needed for relief of menopausal symptoms (including vasomotor instability, sexual dysfunction, mood, fatigue and skin issues) and to prevent long-term health sequel of estrogen deficiency, such as osteoporosis (Gaswami et al, 2005).<sup>37</sup> A wide range of HRT preparations are available for estrogen replacement including oral, transdermal,



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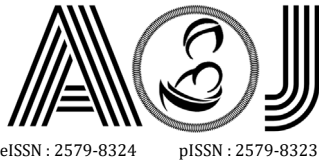
subcutaneous and vaginal routes of administration.<sup>37,39</sup> An HRT regimen should be based on the individual preferences of each patient. Women with POI should be informed that HRT has not been found to increase the risk of breast cancer before the age of natural menopause.<sup>39</sup>

**CONCLUSION**

In conclusion, this study shows that women with epilepsy have an increased risk for developing premature ovarian failure. This finding should be considered in counseling WWE about family planning and in clinical management of WWE. Management of epilepsy in women requires not only knowledge of epilepsy, but also recognition of the various roles and priorities women have in their lives (education, career development, child rearing, the role as carer within the extended family), and attention to gender-specific issues and their impact on patients' wellbeing throughout life.

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