# Management of women with epilepsy

Practical issues faced when dealing with women with epilepsy

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## ABSTRACT

يعد مرض الصرع من أكثر الأمراض العصبية شيوعاً، حيث يبلغ عدد المصابين به أكثر من خمسين مليون شخص في العالم حسب الإحصائيات المنشورة من قبل منظمة الصحة العالمية. وتعتبر حالات الصرع عند السيدات ذات خصوصية نظراً لتأثير العلاج عليهن خصوصاً في فترة الحمل وما بعد الولادة، والآثار السلبية التي قد تنتج عن تعرض الجنين للعلاج قبل الولادة، بالإضافة إلى تأثير التغير الهرموني، والتأثير المتبادل بين أدوية منع الحمل وعلاجات الصرع. تتطلب هذه الخصوصية في العلاج علماً أكثر و خبرة أكبر بالمرض وبالآثار الجانبية على السيدة فترة قبل وما الأعراض الجانبية. سوف نناقش في هذا البحث بعض النقاط الخيوية التي تتعلق بمتابعة وعلاج السيدة المصابة بالصرع، مع التطرق لأمور ذات خصوصية بالسيدة المصابة بالصرع.

Epilepsy is commonly encountered in neurology practice, affecting more than 50 million people worldwide, according to the World Health Organization reports. Management of women with epilepsy requires attention to some considerations including the hormonal changes and its impact on epilepsy, the interaction between oral contraceptives and antiepileptic drugs (AEDs), pregnancy, and the potential teratogenic risk associated with AEDs use during that period. Similarly, the effect of AEDs on bone health should always be considered, and measures should be taken to reduce the risk of osteoporosis given the fact that women in their menopause are at increased risk. Despite the considerable risk of teratogenicity with AEDs use in pregnancy, more than 90% of pregnancies will be uneventful.

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Epilepsy is a chronic neurological disorder seen Commonly in practice, characterized by recurrent unprovoked seizures. The risk of acquiring epilepsy is approximately 3%.1 It is seen in both men and women and among all ages, contributing to 1% of burden of disease, based on disability-adjusted life years - that is; years of productivity lost as a result of disability or premature death.<sup>2</sup> The overall evaluation of patients with epilepsy is similar for both genders, but there are a few considerations that need to be addressed when dealing with women with epilepsy (WWE), and in particular pregnant women. The purpose of this review is to discuss the issues to be considered when treating WWE, which includes the hormonal effect on epilepsy, the potential interaction between oral contraceptive pills and antiepileptic drugs (AEDs), and management of epilepsy during pregnancy, the post-partum period, and menopause. The teratogenic risk of AEDs will also be discussed.

Epilepsy and hormonal changes. The physiological process involved in releasing the sex hormones, estrogen and progesterone, starts in the hypothalamus through the hypothalamic-pituitary-ovarian pathways. It is known that estrogen is proconvulsant, and progesterone is anticonvulsant. This epileptogenic nature of the sex hormones, along with the relative change in the estrogen/progesterone ratio during the menstrual cycle, may lead to seizure exacerbations and an increase in seizure frequency by 2-folds in relation to menstrual cycle, namely, catamenial epilepsy, which is seen in up to 35% of epileptic women.<sup>3</sup> The most common pattern of epilepsy observed is during the perimenstrual phase, when progesterone withdrawal takes place. The second most common pattern is during ovulation, when the estrogen/progesterone ratio is high. Another seizure

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exacerbation pattern noted is during the luteal phase, when progesterone levels are low. Furthermore, changes in AED levels are observed along with the hormonal changes, as these hormones enhance the hepatic metabolism of AEDs, mostly during premenstration, which may lead to seizure exacerbations.<sup>4</sup> There is no approved treatment of catamenial epilepsy, but several approaches have been tried. These include a perimenstrual increase in AEDs doses, or intermittent treatment with acetazolamide or benzodiazepines during the seizure exacerbation period. Such approaches are commonly limited by the side effects of the treatment. Response to natural high-dose progesterone therapy was observed in a few open label trials.<sup>5,6</sup> The use of ganaxolone, an analogue of the GABA<sup>A</sup> receptor modulating progesterone metabolite, was found to be effective in one study, but further confirmatory studies are required.7

Changes in seizure frequency are also observed during the peri- and post-menopause, where some women report an increase in seizure frequency, which may be related to an increase in the estrogen/progesterone ratio. On the other hand, women with catamenial epilepsy usually report a decrease in seizure frequency in the postmenopausal period, when both estrogen and progesterone levels are low.8 Another observation during menopause is that women with epilepsy and frequent seizures are likely to have menopause 3-4 years earlier than those with epilepsy and less frequent seizures.<sup>9</sup> This could be secondary to the chronic abnormalities of central hormone secretion (luteinizing hormone [LH] and follicle stimulating hormone [FSH]) seen in WWE, where inadequate levels of these hormones produce anovulatory menstrual cycles and secondary amenorrhea.

Antiepileptic use and hormonal changes. Alteration of sex hormones in WWE is well addressed in the literature, and the influence of AEDs on the metabolism of the central and peripheral hormones and their biding receptors is observed. One example is the association between the use of hepatic enzyme inducing antiepileptic drugs (EIAEDs), either as a monotherapy or polytherapy, and the presence of low estradiol levels compared to those on non-enzyme inducing antiepileptic drugs (NEIAEDs).<sup>10</sup> On the other hand, sodium valproate (VPA), a NEIAED, is known to be associated with reproductive endocrine disorder, polycystic ovaries, hyperandrogenism, and menstrual disturbance, especially if started before the age of 20 years.<sup>11-13</sup> One of the possible mechanisms through which sodium valproate (VPA) exerts this effect is the elevation of testosterone. Recent data suggest that these changes may be reversible if VPA is discontinued.<sup>14</sup>

There is not enough data to make a conclusion regarding the newer AEDs and reproductive dysfunction. However, lamotrigine (LMT) was evaluated and a lower prevalence of reproductive disorders was found compared with VPA, particularly if used to substitute VPA.<sup>15</sup>

Antiepileptics and oral contraceptive pills. It is commonly encountered that WWE are prescribed oral contraceptive pills (OCP) during their childbearing age. Interaction between OCPs and AEDs is well recognized, which takes place in a number of ways. The EIAEDs enhance the metabolism of the OCP, which increases their hepatic elimination, leading to their failure, and possibly pregnancy. In such cases, a higher dose of estrogen containing pills, 50 µg, should be used, along with other barrier methods to minimize the risk of failure even further. This is applicable with the use of carbamazepine (CBZ), oxcarbazepine (OXC), phenobarbital (PBH), phenytoin (PHT), and higher doses of topiramate (TPM).<sup>16,17</sup> The rest of the AEDs have no, or clinically insignificant effects on the estrogen component of the OCP. Data are very limited on progesterone containing pills, which are not usually recommended for contraception in WWE.<sup>18</sup> The OCPs were found to enhance the elimination of LMT through its hepatic metabolism, which would be seen following the introduction of the pills, leading to increase in seizure frequency.<sup>19</sup> This is related to the estrogen component of the pill, and can be unpredictable. Monitoring of the serum level of LMT is recommended before and following the introduction of the OCP, and higher levels of estrogen may be detected when switching the pills to the progesterone containing ones. The concomitant use of VPA will block the effect of contraceptive pills on LMT.20

*Epilepsy and pregnancy.* The physiological changes associated with pregnancy such as the increase in body volume, altered hepatic metabolism, altered renal clearance, or the change in the gastric motility has a well-recognized effect on the pharmacokinetic of some AEDs and plasma drug levels.<sup>21</sup> On the other hand, the fear of teratogenicity may lead to discontinuation of antiepileptic use during pregnancy. All which may lead to an increased risk of breakthrough seizures, which are not related to a particular trimester. This increased risk of seizure was associated with localization related epilepsy, and seen more in those on polytherapy.<sup>22</sup> The plasma levels of the AEDs may not correlate well with the risk of seizures, but adjustment of the dosing according to the levels was found to help in around 70% of cases in one study.<sup>23</sup> However, increasing the dose in response to the plasma level may increase the risk of teratogenicity and

should be considered with caution. With the exception of LMT and OXC, data are lacking regarding the newer AEDs, and the clinical value of their serum monitoring in pregnancy. With the advantage of a relatively lower or unknown risk of teratogenicity of the newer AEDs, one would assume a relatively safe use of these AEDs without the need for serum monitoring, which will provide more convenience for patients while on these agents during pregnancy.

The management of WWE during pregnancy requires a thorough knowledge of epilepsy and the use of AEDs during this period, to minimize complications of epilepsy or risks of exposure to AEDs. The optimal management plan should start before conception, preferably 9 months before pregnancy. The discussion with the woman should focus on the need for AEDs in pregnancy, but also the possibility of teratogenicity associated with some of the AEDs during the first trimester. The best choice of AED in pregnancy is driven by best response to AED prior to pregnancy. Yet, one should avoid medications known to be associated with a higher risk of congenital malformations. The optimum AED dose can be achieved 6-9 months prior to conception, and conception is preferably delayed until the seizure freedom is achieved on therapy, but the lowest effective dose of that particular AED is the preferred dose. Seizure freedom within 9 months prior to pregnancy is usually an indicator of seizure freedom during pregnancy.

The WWE of a childbearing age are advised to take folic acid supplementation before and during pregnancy.<sup>24</sup> There is evidence of a lower risk of congenital malformations in newborns exposed to AEDs in utero along with folic acid supplementation,<sup>25</sup> with a minimum recommended dose of 0.4 mg/day.<sup>26</sup> The exact optimal dose of folic acid is not known, and there is no convincing evidence to suggest a better protection with higher versus lower doses of folic acid supplementation. It is widely accepted to advise non epileptic women of a childbearing age to receive

North American registry<sup>33,34</sup>

Finnish drug prescription35

Australian Register37

Swedish medical birth registry36

a daily folic acid supplementation prior to and during pregnancy as well.<sup>26</sup>

Finally, the benefit of vitamin K supplementation during the last month of pregnancy in WWE using EIAEDs to reduce neonatal hemorrhage was questioned in a recent study.<sup>27</sup> The American Academy of Neurology has also questioned this in recent practice parameter guidelines published in 2009.<sup>28</sup> It may still be the practice to give vitamin K during the last trimester of pregnancy, with or without the use of EIAEDs.

*Teratogenic effect of antiepileptics.* The teratogenic effect of AED use during pregnancy has been observed since the 1960s.<sup>19</sup> The overall risk of a major congenital malformation (MCM) was 6.1% in children born to WWE using AEDs, 2.8% in children born to women with untreated epilepsy, and 2.2% in the healthy control group.<sup>20</sup> The increased risk of malformation is related to AED use, and not because of epilepsy.<sup>28</sup> The risk is higher with polytherapy than with a monotherapy regimen, with higher doses of AEDs, with low serum folate, and low maternal education.<sup>29</sup>

Cardiac malformations are the most frequent complication noted, followed by hypospadias, facial clefts, and neural tube defects, a pattern similar to one found in a normal population.<sup>29</sup> Most of the AEDs are not associated with a specific malformation, with the exception of neural tube defects seen with VPA and to some extent CBZ.

The recent analysis from the EURAP epilepsy and pregnancy registry<sup>30</sup> showed that the type of AED influenced the risk of teratogenicity, with VPA and PBT being the most teratogenic. That data also showed the association between the dosing of the AED given in the first trimester and teratogenicity, where risks of malformation were significantly higher with VPA and PBT at all investigated doses, and with CBZ at doses greater than 400 mg per day compared to less than 300 mg/day of LMT. The teratogenic risks of selected AEDs when used as a monotherapy from different registries are shown in Table 1. Table 2 shows the pregnancy category of selected AEDs.

LMT

4.5%

3.2%

2.8%

4.9%

1.4%

Registry	VPA	CBZ	PHT	РВТ
EURAP registry <sup>±30</sup>	10.4%*	5.3%†	-	13.7% <sup>‡</sup>
UK registry <sup>31,32</sup>	6.2%	2.2%	3.7%	-

10.7%

10.6%

7.7%

13.3%

Table 1 - Antiepileptics and risk of teratogenicity.

VPA - valproic acid, CBZ - carbamazepine, PHT - phenytoin, PBT - phenobarbital, LMT - lamotrigine, TMP - topiramate; <sup>‡</sup>Findings with moderate to high dosing shown, <sup>\*</sup>with a daily dose ranging between 700-1500 mg, <sup>†</sup>with a daily dose more than 150 mg, <sup>§</sup>with a daily dose more than 300 mg

2.6%

7.6%

3.2%

6.5%

2.5%

2.7%

5.4%

3.0%

TPM

2.4%

Table 2 - Pregnancy category and selected antiepileptics.47

Antiepileptic	Pregnancy category		
Carbamazepine	D		
Clonazepam	D		
Lacosamide	С		
Lamotrigine	С		
Levetiracetam	С		
Phenobarbital	D		
Phenytoin	D		
Topiramate	D		
Valproate	D		

D - Category D. There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. C - Category C. Animal studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

The management of the WWE during pregnancy should include continuation of AEDs despite the low risk of teratogenicity, since the risk of seizures on both the maternal and the fetal side could result in serious injuries. Unnecessary changes of AEDs during pregnancy should be avoided, particularly if seizure control is achieved prior to pregnancy. Drug levels should be monitored closely in each trimester, especially for PHT, LMT, and CBZ,<sup>37</sup> aiming to achieve the lowest effective dose. Monotherapy should be used, and if polytherapy is required, one should avoid combining AEDS known to have a high teratogenic risk. Valproic acid should be avoided in WWE prior to a planned pregnancy, if possible, and during the first trimester of pregnancy, and other AEDs should be strongly considered. If VPA is necessary, the lowest effective dose should be used. Polytherapy should be avoided during the first trimester, particularly one that includes the use of VPA. A daily folic acid supplementation (1-5 mg) should be given to all women of a childbearing age, and during the pregnancy.

The risk of cognitive teratogenicity and outcomes of children exposed to AEDs in utero were evaluated, and it was found that exposure to VPA, PBT, and PHT in utero was possibly associated with poor cognitive outcomes, compared to other AEDs such as CBZ.<sup>38-40</sup> The poor cognitive outcome was slightly increased with polytherapy compared to monotherapy during pregnancy. It is prudent to consider the cognitive teratogenic effect of AEDs in WWE during pregnancy, and avoidance of such AEDs is advisable.

Detecting the major malformations in pregnancy, particularly neural tube defects, will require high quality ultrasound of the fetus, measurement of  $\alpha$ -fetoprotein and acetylcholinesterase levels at weeks 15 and 18, all of which can detect 99% of the major malformations. In the event of inconclusive results of the former investigations, amniocentesis should be carried out. Despite the aforementioned facts, more than 90% of pregnancies will be uneventful.<sup>41</sup>

*Epilepsy during delivery and post-partum.* The risk of seizures during labor was found to be 3.5%, and it correlates with the number of seizures during pregnancy.<sup>42</sup> If a seizure develops, it should be managed with intravenous benzodiazepines such as lorazepam or diazepam, and status epilepticus should be managed accordingly, once it is diagnosed. The pediatrician should be available, especially if over sedation of the newborn was observed in association with AED administration. Otherwise, the diagnosis of epilepsy dose not require child birth through cesarean section, unless there is increased seizures that put either the mother or the fetus at risk, or when the mother cannot proceed with normal labor after receiving a sedating AED.

The mother should be educated regarding the factors known to lower seizure thresholds, such as sleep deprivation, something experienced very often by a lactating mother, and these should be minimized or avoided if possible. She should also be instructed regarding breastfeeding the baby while sitting or lying on the floor, and to change the baby while placing him on the floor. The epileptic mother should not bath the baby alone. The aforementioned measures will help to avoid injuries to the newborn if the mother develops a seizure while caring for him.

All AEDs are inadvertently secreted in breast milk, with variable concentrations and significance, although the neonatal level of the used antiepileptic does not correlate with levels in the milk. The AEDs should be continued early after birth and during the post-partum period, and mothers are not advised to quit breastfeeding while using AEDs. One regimen to reduce the amount of AED passed to the newborn is to take the medication after breastfeeding the baby. The evidence is lacking regarding the effect of ingested AEDs on the newborn from maternal milk. The AEDs known to cause sedation such as benzodiazepines should be avoided, since they were found to cause over sedation of the newborns of the lactating mothers.<sup>43</sup>

*Epilepsy, antiepileptics, and bone health.* The WWE may continue to have seizures throughout their different stages of life, and the requirement of AEDs for longer periods may alter the bone mineral density (BMD), subsequently leading to osteoporosis, something they are more likely to be affected by during the post menopausal period. This would increase their risk of fractures secondary to multiple factors including seizure related falls, longer duration of epilepsy, and the use of

AEDs. Phenytoin, PBT, CBZ, and VPA are associated with a reduced BMD, and this risk is potentiated by polytherapy.<sup>44</sup> Data are still scarce regarding the newer AEDs and their effect on bone density.

A daily supplement of vitamin D starting at 400 IU was found to increase the BMD in those with epilepsy and on AEDs, and higher doses (4000 IU per day) were found to be even more effective to restore the BMD, especially if receiving EIAEDs.<sup>45</sup> Vitamin D supplementation should be advised for patients with epilepsy, and in particular WWE because of the aforementioned factors.

In conclusion, the management of WWE continues to be an interesting, yet sometimes challenging task that requires a good knowledge of the issues commonly encountered when treating WWE. Gender issues should be kept in mind as well for the possibilities of the interactions between the sex hormones and AEDs. Epilepsy during pregnancy will continue to be a hot topic of great clinical significance. Controlling seizures is the goal, which should be carefully achieved in WWE by either withdrawal of AEDs prior to conception if clinically indicated, or continuing a monotherapy regimen using the lowest effective dose during pregnancy. The risk of teratogenicity of AEDs and the potential complications of seizures during pregnancy should also be elaborated. Finally, restoring bone mineral density using vitamin D supplementation is recommended in WWE using AEDs, especially hepatic enzyme inducers.

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