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Clinical guideline: epilepsy in pregnancy and women of childbearing age

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Abstract

Childbearing-aged and pregnant women undergo physiological modifications that make them think in a particular way about epilepsy and the management of taking antiepileptic drugs. These guidelines address both the effects of epilepsy in the gynecological, obstetric, and perinatal aspect of the woman, with a series of recommendations based on evidence-based medicine.

Key words: *Epilepsy. Woman. Childbearing age. Pregnancy.*

Introduction

Epilepsy in reproductive-aged and pregnant women entails a series of reproductive changes, such as interaction of antiepileptic drugs (AEDs) with contraceptives, changes in fertility, changes inherent to pregnancy and hormonal modification, a series of risks for congenital malformation caused by AEDs, and obstetric and lactation modifications that require knowledge and recommendations necessary for an adequate control of epileptic seizures (ES) in women with epilepsy (WWE). This is the main reason for the PPE to write these guidelines.

What are the recommendations for childbearing-aged WWE?

According to statistics published by the National Institute of Statistics and Geography, in Mexico, there are 61.4 million women, and they represent more than half of the nation's population (51.4%)[1]. Many of them are of childbearing age and have high probabilities of becoming pregnant.

The AEDs that are enzymatic inducers (EI-AED) (PHT, TPM, PB, OXC, and CBZ) directly modify hormone concentrations. Virtual payment address (VPA) is associated with an increase in serum testosterone

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and risk of hirsutism, central cause amenorrhea, hyperandrogenemia, and infertility. The risk of infertility can be up to 10% greater than those of the general population and is greater with polytherapy, with temporal lobe epilepsy, and the use of PB[2]. AEDs have a bidirectional relationship with hormonal contraceptives3. There are variations in serum concentration of AED, depending on the mechanism of action of the drug and the type of contraceptive[4]. According to the WHO and the CDC, progesterone and combined oral contraceptives, as well as contraceptive patches and vaginal rings are not recommended as first-line contraceptives for women that take EI-AED. Medroxyprogesterone and levonorgestrel implants can be used by women who take EI-AED. It is recommended to avoid combining LMT and contraceptive methods that contain estrogens, due to the risk of loss of control of ES. The IUD is recommended as the contraceptive of choice for WWE[5].

Should AED treatment be suspended in pregnant WWE (PWWE)?

A review published by the AAN in 2009, did not find studies with high levels of evidence that indicate changes in the frequency of ES during pregnancy, but information is limited. There is between 84 and 92% probability that the pregnancy will continue normally with proper control if the WWE has been seizure-free for 9-12 months before getting pregnant[6].

For PWWE, the use of AED in monotherapy and at low doses is suggested. Preferably, AEDs with a greater risk of teratogenicity should be avoided, such as VPA, which has been demonstrated to increase this risk up to 13.8%[7]. The greatest risk of congenital malformations is considered to be during the first trimester of pregnancy, so once neural tube formation is completed (second and third trimester of pregnancy), the contraindication to suspend VPA is relative, and generally, the change of an AED during pregnancy is not recommended due to the risk of uncontrolled ES[8]. PHT, PB, and TPM have been demonstrated to have an intermediate risk of congenital malformations, whereas LTG, CBZ, and LEV show low rates of such malformations[7]. The frequency of ES is increased when patients discontinue the use of their AED, so patients must have control of the ES and discipline in taking their AED. It is frequent that PWWE suspend their AED for fear of the risk of congenital malformations of the fetus, due to nausea and vomiting associated to pregnancy, the pharmacokinetic changes of the AED, and insomnia; it is even frequent that treating physicians suspend AED, even in spite of this being counterproductive, since it has been demonstrated that during a ES the fetus suffers anoxia, fetal tachycardia, uterine contractions, increased risk of preterm labor, and low birth weight. One Canadian study demonstrated that up to 30% of neurologists are unaware of the obstetric complications of PWWE. Thus, we can infer that the OB/GYN is also unaware of treatment complications for PWWE[9-11].

A planned pregnancy demonstrates that there is better control of the ES and shows apparent improvement in the obstetric complications of labor.

Which AED should be used for the PWWE?

There is no first choice AED for the PWWE, and the AED must be adequate for the type of epilepsy suffered by the patient. There have been major congenital malformations (CM) described in products of those PWWE that took EAD during their pregnancy. In these cases, structural CM have been reported, such as hypospadias, neural tube defects (NTD), congenital cardiopathy, and cleft palate. Long-term cognitive teratogenic effects are also observed in children whose mothers took AED during pregnancy, although the studies are not conclusive[7]. The risk of CM with AED varies depending on the type of AED used, the dose, and whether it was used in mono or polytherapy. In general, the average risk of CM with AED varies between 4 and 14%, while in the open population risk of CM is about 3%. The risk of CM with CBZ is about 2.2%, LMT is 3.2%, PHT is 3.7%, and it is >13% for VPA. It must be pointed out that combining CBZ with LMT has a 3% risk of CM. When polytherapy includes VPA, the risk of CM can increase to up to 13.8%, especially for NTD. For WWE who have had a product with a CM, the risk of CM in subsequent pregnancies with the use of AED increases up to 16.8%. During pregnancy, serum levels of CBZ, LMT, PHT, and LEV are reduced; thus, serum concentrations of these AED must be determined before conception and during the first trimester of pregnancy. In developed countries, the most commonly used AED are LMT, and LEV, and in our Country, CBZ is considered to be the most commonly used as well as, paradoxically, VPA[11-13].

What is the approach and treatment for uncontrolled ES in PWWE?

The presence of ES during pregnancy could be due to three circumstances: uncontrolled ES in PWWE,

debut of ES, and obstetric problems. The first of these circumstances is the most common, and the main reason is the lack of compliance with the antiepileptic treatment; this commonly happens to PWWE, and so one must investigate and persuade therapeutic adherence. Other factors must be taken into consideration, such as genetic factors, changes in serum concentrations of AED, sleep suppression, stress, and hyperemesis gravidarum induced by pregnancy. The management of uncontrolled ES in PWWE must follow the same protocol as that of any other patient with epilepsy. Despite the seriousness of ES, they do not increase in frequency in PWWE.

Once the ES are controlled, one must restart the AED the patient was taking, if the motive was lack of discipline. In this case, adjust the AED treatment depending on the type of epilepsy and with the adequate dose[14,15].

What are the obstetric complications for PWWE?

There is a dilemma in terms of the increase in obstetric risk in PWWE. Previously, there was no evidence that confirmed it, but recent studies have demonstrated a risk of presenting preeclampsia, maternal infection, placental abruption, emergency cesarean sections, risk of fetal death, abortions, neonatal infections, risk of neonatal asphyxia with Apgar lower than 5 points in the 1st min, neonatal hypoglycemia, and neonatal hypoxia[16,17].

What is the utility of folic acid and Vitamin K in PWWE?

One of the most frequent congenital malformations of the CNS is NTD. Folate receptors are critical for fetal neural tube and neural crest formation. Folate deficiency causes a reduction in the mitotic capacity of neural crest or neural tube cells. Folic acid is the synthetic form of folate (Vitamin B9). Mexico is one of the countries with the greatest frequency of NTD. The worldwide recommendation (WHO) is that childbearing-aged women supplement with 0.4-0.8 mg of folic acid daily since it is calculated that 75% of them do not consume the optimal dose of folic acid. However, for NTD prevention, the dose is greater. There is no consensus on the larger dose; the objective is to achieve high tissue levels of folic acid in the 1st weeks of pregnancy, during the time that the neural tube is formed.

As a large percentage of WWE have unplanned pregnancies, it is recommended to take folic acid daily; it should be taken for at least 1 month before conception if pregnancy is planned and should continue at least during the first trimester. It is considered that, in addition to the reduction of NTD, the development of other malformations, such as cleft palate, can also be reduced.

If there is a history of an infant with NTD, the daily recommendation is 4 or even 5 mg of folic acid, since there are no adverse effects related to this vitamin. It has been calculated that this results in a reduction in NTD of up to 85%. This recommendation is especially important for WWE that take polytherapy or use VPA[18-20].

As for Vitamin K, it was previously proposed that by giving doses of the said vitamin to PWWE during the third trimester, you could prevent intracranial hemorrhaging in neonates. It was thought that PWWE that took enzymatic inducing AED (CBZ, PG, and PHT) had increased risk of this hemorrhagic complication in their products. In a study of more than 600 patients, it was demonstrated that there was no increase in the risk of hemorrhages in the products of PWWE that took these AED compared to controls; thus, there is not sufficient evidence to recommend the use of Vitamin K in PWWE[7,21].

Is breastfeeding safe in WWE?

The benefits of maternal breastfeeding are well demonstrated, it's even beneficial for the mother since it reduces the risk of postpartum depression as well as generating a psychologic bond with the infant conversely, the BBB in neonates has not been completely formed; thus, it is susceptible to drugs. Therefore, there must be an adequate risk-benefit analysis.

Patients get confused because they receive information from the obstetrician, the neonatologist or the neurologist, this in conjunction with the social concept that the WWE cannot breastfeed. Studies show that breastfeeding has geographical variations, at educational levels, and is lower among WWE that take LMT or are receiving polytherapy.

The concentration of an AED in maternal milk is dependent on the serum levels of the drug and the metabolism of the infant. Although there are mathematical formulas to calculate AED concentrations in maternal milk, it is not practical to use this method in daily practice. Furthermore, the AED concentrations are different and individual for each AED.

There are studies that aim to investigate the cognitive effects on children exposed to AEDs during breastfeeding, but the results are contradictory.

The recommendations from the AAN, in 2009, about breastfeeding were not conclusive, and later studies have not demonstrated the existence of contraindications for

breastfeeding by WWE. What is clear is that the serum levels of AED that the WWE is taking must be measured, that there is the option of supplementary feeding if secondary effects are suspected for the infant, and that breastfeeding is preferred when the newborn has long sleep patterns. The infant should be observed to determine excessive sleepiness, and both the benefits to the mother of avoiding postpartum depression and the harm that sleep deprivation may cause to the WWE must be assessed[22-24].

Evidence tables and recommendations

Evidence and PPE recommendations	Level/recommendation
There is increased infertility and sexual dysfunction in WWE.	III
The frequency of gynecologic disorders is greater in WWE.	III
WWE that take hormonal contraceptives must be under medical surveillance.	III
Health professionals must be aware that WWE have reduced fertility and libido.	R-PPE
The presence of polycystic ovaries, hirsutism, galactorrhea, and central cause amenorrhea is more frequent in WWE.	R-PPE
IUD is recommended as a contraceptive method for WWE.	R-PPE

Evidence and PPE recommendations	Level/recommendation
There are no modifications in ES in WWE during pregnancy if the patient does not suspend treatment.	III
Planned pregnancy for WWE reduces the risk of ES during pregnancy.	III
Most pregnancies in WWE are not planned; thus, it is recommended to provide preconception information to reproductive-aged WWE about the effects of AED on the infant.	II
Uncontrolled ES occur due to discontinued AED treatment, basically due to a lack of awareness about the risks of teratogenicity of these drugs.	I
WWE can have a normal pregnancy, especially if before conception (at least 9 months) there is good control of ES.	R-PPE
WWE must not suspend their antiepileptic treatment during pregnancy.	R-PPE
Changing the epileptic treatment scheme during pregnancy is not recommended due to the risk of uncontrolled seizures.	R-PPE
Management of WWE must be multidisciplinary, and all physicians must be aware of the risk of teratogenicity from AED.	R-PPE
Determining the serum concentrations of AED during the first trimester of pregnancy is recommended. There is no consensus for the following trimesters.	R-PPE

Evidence	Level
There is no AED of choice for the PWWE, and the adequate AED for the subtype of epilepsy suffered by the patient must be used.	I
Monotherapy and lower effective therapeutic doses are preferable.	II
After the first trimester of pregnancy, there is no evidence that the use of AED poses a greater risk of CM.	II
The risk of CM with AEDs varies between 2% and 13.8% and occurs more often with VPA.	II
There is no sufficient data on the safety of the new AED and the risk of CM.	II
A reduction in the dose of AED in PWWE must be after having been seizure free for a minimum of 3 years.	II
The ideal AED must be used for the type of epilepsy suffered by the PWWE.	R-PPE

All AEDs have some risk of CM.	R-PPE
The knowledge of the risk of CM is greater for the classic AED than for the new AED.	R-PPE
The main risk for CM with AED happens during the first trimester of pregnancy; during the rest of the pregnancy, risks are low.	R-PPE
The use of VPA is not recommended for PWWE; if used, it must be at the lowest therapeutic dose.	R-PPE
For WWE that plan to get pregnant, using CBZ, OXC, LEV, or LMT is recommended.	R-PPE

Evidence and PPE recommendations	Level/recommendation
The main cause of ES during pregnancy is due to a lack of pharmacologic discipline.	II
If focal neurologic data exist, the PWWE must undergo a profound investigation (MRI, EEG, and NS)	I
Control of ES during pregnancy must adhere to the same recommendations as conventional ES.	III
The frequency of ES does not increase in PWWE.	III
It is recommended to insist that the PWWE be disciplined in taking the antiepileptic treatment.	R-PPE
Management of ES in PWWE must adhere to the same guidelines as in non-pregnant patients.	R-PPE
One must pay attention to the neurologic integrity of the PWWE that has ES.	R-PPE
The frequency of ES in PWWE is the same as in the epileptic patient, but its important to know how to diagnose it due to its gravity.	R-PPE

Evidence and PPE recommendations	Level/recommendation
The risk of presenting obstetric complications (placenta previa, preterm labor, cesarean section, and preeclampsia) during pregnancy in the PWWE, does not appear to differ from the rest of the obstetric patients.	III
The risk of presenting complications to the infant (neonatal hypoxia and hypoglycemia, and risk of infection) of the PWWE, does not appear to differ from the rest of the obstetric patients.	III
There is no certainty about the increased risk of obstetric complications in PWWE.	R-PPE
There is no certainty about the increased risks to a newborn child of a WWE in relation to neonates born of a non-epileptic mother.	R-PPE
Its recommended to keep close vigilance on PWWE during gestation, labor and puerperium, faced with the possible risk of complications. The same must apply for the children of a PWWE.	R-PPE

Evidence and PPE recommendations	Level/recommendation
Folic acid is necessary for the formation of the neural tube.	I
Daily ingestion of folic acid in reproductive-aged women is much lower than the daily recommended nutritional requirement.	I
A daily dose of 0.4-0.8 mg of folic acid reduces the risk of NTD. In WWE with a history of NTD, use of polytherapy or VPA, greater doses are required.	I
There is no evidence to support that prophylactic doses of Vitamin K in PWWE protect their neonates from intracranial hemorrhages.	III
All PWWE should consume 0.4-0.8 mg of folic acid every day.	R-PPE
All WWE and a history of NTD, polytherapy, and VPA use must consume 4-5 mg of folic acid daily to reduce the risk of NTD.	R-PPE
Prophylactic doses of Vitamin K are not recommended for PWWE.	R-PPE

Evidence and PPE recommendations	Level/recommendation
Evidence	**Level**
The benefits of breast milk are accepted worldwide.	I
The concentration of AED in breast milk of a WWE, essentially depends on the serum concentration of the drug.	II
Unless there is clinical evidence of neonatal secondary effects (sleepiness and others), WWE should not suspend breastfeeding.	III
WWE must breastfeed without clinical contraindications unless the neonate presents secondary effects.	R-PPE
One must be careful about breastfeeding when WWE are taking PB, BZD, or are undergoing polytherapy.	R-PPE
Unless there is clinical evidence of neonatal secondary effects (sleepiness and others) breastfeeding should not be suspended in WWE.	R-PPE

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