

eISSN : 2579-8324

pISSN : 2579-8323

Alamat Korespondensi:

Ruang Redaksi Andalas Obstetrics and Gynecology Journal, Lantai 3 PPDS Obstetri dan Ginekologi Universitas Andalas, RSUP DR. M. Djamil Padang, Jl. Perintis Kemerdekaan Padang, Sumatera Barat 25127

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LITERATURE REVIEW

Selecting Hormonal Contraceptives in Women Taking Antiepileptic Drugs : Review of Literature and Practical Recommendations

Hendra Permana¹, Restu Susanti¹, Syamel Muhammad²

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

Correspondence: Hendra Permana, email: saint_check_lie@yahoo.com, Hp: 081534302954

Abstract

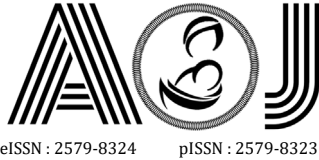
Contraception is a very important issue in women with epilepsy, since very broad questions taken in applying it to prevent unplanned pregnancy. The choice of contraceptive methods must be related to how the mechanism of action of antiepileptic drugs (AEDs), the contraceptive itself, and both interactions. Hormonal contraception can induce metabolism of AEDs and lead to increasing of seizure frequency, and in the other hand AEDs may decrease the blood levels of hormonal contraception. Therefore, physician must consider the type of contraception being used before prescribing AEDs. Additionally, they should emphasize the interaction between them in counseling, to assure that women with epilepsy have time to decide which type will be best use for them. This challenging matter needs better recommendation for practice, both neurologist and gynecologist.

Keywords: antiepileptic drug, contraception, women with epilepsy

INTRODUCTION

The global prevalence of epilepsy is about 1% of the population over the world. About a half of this proportion are women. It is estimated that about 1,5 million of them were women at reproductive age.¹ Some problems may occur in their group during this period including hormonal changes, pregnancy, perinatal periods, lactations, and contraceptive use. The issues will bring consequences to the sufferer like unplanned pregnancy, teratogenic effects of antiepileptic drugs (AEDs), and increasing seizure as a result of hormonal change.^{1,2}

Despite most of the women with epilepsy receive adequate information regarding pregnancy and seizure, they do not get adequate counselling about contraceptive use. A 2015 survey reported that <7% of women received contraceptive counseling. This situation is worse in developing country where the couple seldom discussing this matter because of shyness as well as privacy issue in clinical setting.² Otherwise, doctors also ignore the importance of counselling because they have full schedule as well as lack of knowledge regarding the choice of contraception in women taking AEDs.^{2,3} They tend to disobey the advise from the World



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Health Organization (WHO) about medical eligibility criteria for the prescription of contraceptive methods among women with epilepsy.¹

Patients using AEDs may have a challenging situation regarding hormonal contraception. Inappropriate use of hormonal contraception may affect the pregnancy itself and increase the possibility of subsequent seizure. In other hand, it also increase the risk of teratogenicity for pregnant women who take AED.¹⁻⁴ Additionally, the inappropriate co-prescription of AED and hormonal contraception can result in reduced bioavailability of both drugs.⁵ Unfortunately, the frequency of contraceptive use failure in women taking AED is quite common. Reimers et al (2015) reported that one in four unplanned pregnancy was caused by the failure of oral contraceptive,⁵ while Herzog et al (2016) reported that 69,6% women with epilepsy were at risk of unplanned pregnancy, eventhough they used contraceptive.⁴

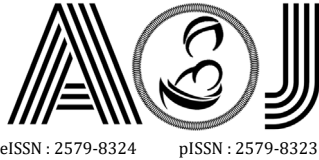
HORMONAL CONTRACEPTIVES AND RISK OF SEIZURE

The use of hormonal contraceptives do not increase the risk of seizure based on several studies. Otherwise, the oral contraceptive use has been documented to alleviate seizure caused by menstruation. A study reported that progestogen use may effect the decreasing seizure frequency in women with intractable epilepsy or catamenial epilepsy. However, there still a little doubt whether the use of oral contraceptive may exacerbate the seizure and needs future study to clarify the issue.^{2,5,6}

Some evidence grow with the link between steroid hormones and neurosteroids and seizure susceptibility. Nonetheless, there is limited information regarding potential impact of oral contraceptives on seizure in women with epilepsy.⁶ A recent study suggests that oral contraceptive may exacerbate seizures, but previous study didn't support this statement.⁷ The reports from Herzog and colleagues (2015) stated that hormonal contraception use may increase the risk of seizure (28,2%) compared to non hormonal one (9,7%). An interesting point taken from this study is that women using hormonal contraceptives will have relative risk about 4,5 times of increasing seizures compared to those with non hormonal types.⁷

How the hormonal contraceptives may increase epileptic seizures remain questioned. There is lack of evidence about neuroactive properties of the synthetic steroid compund of oral contraceptives. Reproductive steroids have neuroactive properties that can modulate neuronal excitability and seizure thresholds. Some AEDs possess reciprocal interactions with hormonal contraceptives, so the effects may hamper both medications.^{7,8}

Another consideration is non oral progesterone contraceptives may have less effect on seizure frequency compared to hormonal patch and progestin-only pills.^{6,7} Progesterone has antiseizure properties. However, the outcome of phase III clinical trial of progesterone therapy couldn't meet the expectation. The study assessed the benefit of progesterone



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therapy in women with intractable epilepsy.⁷ Beyond that, progesterone treatment offered little significant efficacy in reduction seizure frequency, but the good result achieved by women with perimenstrual catamenial exacerbation, whom seizure frequency is significantly reduced. This suggests the benefit of progesterone to treat women with perimenstrually exacerbated seizures.^{6,7}

WHAT AEDS' EFFECTS OF TO HORMONAL CONTRACEPTION

Various contraceptive methods have been proposed nowadays. Especially the hormone based method such as combined oral contraceptive pills, combined contraceptive patch, combined contraceptive vaginal ring, progesterone only pill, progesterone implant, and postcoital contraception. All these methods are based on progestogen and estrogen mechanism of action. However, their use is limited to women with epilepsy because of two way pharmacokinetic interaction with several AEDs.⁸⁻¹¹

The most widely used contraceptive methods include oral contraceptive pills due to high efficacy. This drug inhibits ovulation process by suppressing gonadotropins through feedback action of estrogen and progestogen. Also they induce changes in cervical mucus and endometrium, making the milieu become less conducive to sperm transport as well as fertilization and implantation.⁹

The estrogen compound for all combined oral contraceptives is 17-ethinyl estradiol (EE). Combined oral contraceptive preparations contain 20 to 35 mg of EE and less than 1 mg of progestogen.⁹ This substance is extensively metabolized in first pass metabolism. More than 30% will undergo the metabolism in gut wall, and subsequent biotransformation is catalyzed by cytochrome P450 (CYP), uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 and sulfotransferase (SULT). Most of EE is hydroxylated into inactive metabolites which is catalyzed predominantly by CYP3A4.^{9,11,12} They then undergo conjugation by UGT and SULT, and are subject to enterohepatic re-circulation. EE is a moderate inhibitor of various CYP enzymes, so it can increase the serum concentration of many other drugs significantly.¹¹

AEDs that may potentially impair contraceptive safety of hormonal contraceptives via an increased clearance of the synthetic steroids include the "strong CYP3A inducers" carbamazepine, phenytoin, phenobarbital and primidone as well as the "mild CYP3A inducers" like oxcarbazepine, topiramate and felbamate (Table 1).¹² Although earlier data did not show an effect of lamotrigine on contraceptive safety, a recent pharmacokinetic study in healthy women revealed a clinically relevant influence of 300 mg lamotrigine daily on a combined oral contraceptive (COC) with 30 mg ethinylestradiol and 150 mg levonorgestrel: the area under the curve (AUC) and the maximal plasma concentration (C_{max}) of the levonorgestrel decreased whereas the ethinylestradiol pharmacokinetics were unchanged by lamotrigine. FSH and LH (luteinizing hormone) concentrations increased (by 4.7-fold and 3.4-



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fold) demonstrating a reduced suppression of the hypothalamic—pituitarian axis.^{11,12} Although measurement of serum progesterone showed no evidence of ovulation, contraceptive safety cannot be guaranteed, especially if higher lamotrigine doses and other COCs containing different progestins are used.^{12,13}

The consequences of the drug interaction are a risk of contraceptive failure and unintended pregnancy.^{11,12} Women who are prescribed drugs with a enzyme inducing potential, have therefore been advised to use high-dose oral contraceptives with a dose of the estrogen compound of at least 50 mg (low-dose topiramate monotherapy 35 mg) and should be advised to use additional barrier methods of contraception, especially in case of intramenstrual bleeding.¹³

Data available today suggest that neither of the other newer AEDs; gabapentin, levetiracetam, tiagabine, vigabatrin or zonisamide influence the metabolism of oral contraceptive and can be administrated without risk of contraceptive failure. One study has demonstrated a modest and probably not clinical relevant decrease of the levonorgestrel compound of the oral contraceptives during lamotrigine but no change in the pharmacokinetic parameters of ethinylestradiol.¹²

Table 1. List of AEDs that may interact with hormonal contraceptives¹²

AEDs that may reduce the hormonal contraceptive blood levels	AEDs that do not affect the hormonal contraceptive blood levels
Carbamazepine	Acetazolamide
Felbamate	Benzodiazepine
Lamotrigine	Ethosuccimide
Oxcarbazepine	Gabapentin
Phenobarbital	Lacosamide
Phenytoin	Levetiracetam
Primidone	Pregabalin
Rufinamide	Sodium valproate
Topiramate	Tiagabine
	Vigabatrin
	Zonisamide

INTERACTION OF HORMONAL CONTRACEPTIVES WITH AEDS

Some AEDs induce the activity of cytochrome P450 enzyme, therefore will increase the metabolism rate of EE and progestogens, and subsequently lowering blood levels of these hormones into 50% or more (Table 2).¹² However the effect depends on individual variations.⁹⁻¹³

Oral contraceptives can increase the metabolism of glucuronidated drugs by induction of the uridine diphosphate glucuronosyltransferase system. This has been most intensively studied for lamotrigine which is hepatically metabolized primarily by glucuronic acid



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conjugation. Several studies have demonstrated that lamotrigine is significantly and substantially ($>50\%$) increased by combined oral contraceptives, so this interaction is associated with increased seizure frequency in most of the cases.¹¹⁻¹³

Table 2. Method of contraception in conjunction with enzyme inducing AEDS¹²

Method of contraception that are affected by enzyme inducing AEDs	Method of contraception that are not affected by enzyme inducing AEDs
Combined oral contraceptive pill	Medroxyprogesterone acetate injection depot
Combined contraceptive patch	Levonorgestrel releasing intrauterine system
Combined contraceptive vaginal ring	Other intrauterine contraceptive devices, all copper containing
Progestogen only pill	Barrier methods
Progestogen implant	
Postcoital contraception	

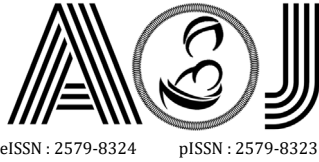
Lamotrigine comedication with an ethinylestradiol containing hormonal contraceptive results in significant decrease of lamotrigine levels. During the period “on the pill”, combined oral contraception causes lamotrigine levels decrease by approximately 50%, followed by an increase of lamotrigine levels up to 80—100% of the baseline in the contraceptive-free week. This is often clinically relevant and may result in an increased risk of seizure recurrence especially in week 2 and 3 “on the pill” or the occurrence of adverse effects at the end of the pill-free interval.^{11,12} These fluctuations are most likely due to an induction of UGT1A4, the enzyme responsible for the glucuronidation of lamotrigine, by ethinyl estradiol.¹²

Valproate levels also seem to be reduced by the concomitant use of hormonal contraceptives. Estrogen contain hormonal contraceptions may increase the metabolism of valproate so it seems to increase seizure frequency in women taking this type of contraception.¹¹ Just as with lamotrigine, the magnitude of observed fluctuations of the valproate levels appear to vary interindividually.^{11,13}

The contraceptive-induced pharmacokinetic alteration shows a considerable inter-individual variability based on probably both genetic factors and co-administration with other AEDs. This can be exemplified by the results in a recent study that revealed that the OC induction of lamotrigine elimination was almost eliminated when co administered with valproate.¹³

CONTRACEPTIVE RECOMMENDATIONS FOR WOMEN WITH EPILEPSY

According to consensus from the World Health Organization (WHO) working group and the Center for Disease Control (CDC), combined oral contraceptive pills and progesterone only pills as well as contraceptive patches and vaginal rings are not recommended as first line choice for women with epilepsy who take enzyme induced AEDs.¹⁴ Therefore, the use of



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depot medroxyprogesterone and levonogestrel implant could be alternative way of contraception. However it has been reported that levonogestrel implant often fail to avoid pregnancy when combined with enzyme induced AEDs.^{13,14}

Another choice of contraceptive method for women with epilepsy is intrauterine device (IUD). It is an effective way to avoid drug-drug interactions between contraception and AEDs.¹⁴ Additionally, the IUD has very high chance of successful program of birth control, with failure rate of 0,2 – 0,8% per year. It is superior compared to most hormonal contraceptive methods and non hormonal barrier methods. The IUD does not require consistent compliance as is needed with barrier methods or the depot medroxyprogesterone injection.¹⁵ Future benefit can be achieved in term of long time use without worry, since the copper IUD last for 10 years, and the 52 mg and 13,5 mg levonorgestrel IUD is approved for 5 and 3 years respectively.^{15,16}

Lamotrigine combination with estrogen containing birth control methods may increase the risk of uncontrol seizure.¹³⁻¹⁵ Since the ethinylestradiol-induced decrease of lamotrigine levels may occur very rapidly only a few days after the hormonal contraceptive was started, it appears to be reasonable to start lamotrigine dose adjustment shortly after the initiation of the hormonal contraception. In the majority of cases approximately a doubling of the initial lamotrigine dose is needed to stabilize lamotrigine levels.¹³ But WHO and CDC advise not to combine lamotrigine with combined hormonal contraceptive methods.¹⁵



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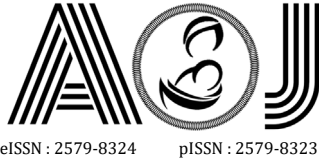
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Table 3. Contraceptive methods, efficacy and consideration for women with epilepsy¹⁴

Contraceptive method	Pregnancies per year	Considerations for women with epilepsy
Intrauterine device (IUD)		
Copper IUD	<1%	No significant AEDs interactions
Levonorgestrel releasing IUD	<1%	Levonorgestrel releasing IUD reduces or eliminates menstrual bleeding
Combined hormonal contraception		
Combined oral contraceptive pills	9%	Not recommended with enzyme inducing AEDs Will reduce lamotrigine levels
Vaginal ring	9%	May be used to treat symptoms of polycystic ovary syndrome
Transdermal patch	9%	Transdermal patch may worsen seizure control
Progesterone only contraception		
Etonogestrel implant	0,05%	Efficacy of the etonogestrel implant may be reduced by enzyme inducin AEDs
Depot medroxyprogesterone acetate injection	6%	The depot medroxyprogesterone acetate injections may offers seizure control benefit in some patients if amenorrhea achieved The depot medroxyprogesterone acetate injection is associated with reversible bone loss Progesterone only pills require excellent compliance
Progesterone only pills	9%	Progesterone only pills is ireduced by enzyme inducing AEDs and possibly lamotrigine and perampanel

Counseling women with epilepsy about drug interactions and contraception is necessary to prevent unintentional pregnancy and avoid breakthrough seizures.¹⁶ However, there are no guidelines stating who is responsible for relaying this critically important information to the patient.¹⁷ A neurologist should never forget to ask a women, if and what type of contraception she is using before prescribing an AED. The decision, which AED to use, or which contraceptive method is optimal for an individual woman with epilepsy depends on a variety of factors. The bidirectional interactive potential of AEDs and hormonal contraceptives needs to be taken into account when counselling women with epilepsy.¹⁶ Alternatives such as the use of an IUD should be kept in mind if standard hormonal contraceptives not appear to offer the contraceptive safety, that is wanted in an individual patient or if potential side effects of the contraceptive method do not warrant their use.¹⁴⁻¹⁶



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CONCLUSION

The selection of contraceptive method to prevent of unplanned pregnancies in women with epilepsy is challenging, especially related to AED use and the risk of breakthrough seizure. For AED use, the dose should be kept at the lowest prescription needed as it can control seizure with no side effect. If necessary, changing AED ideally be initiated at least 1 year before conception. Changing AED after pregnancy may offer little risk of major congenital malformations.

Contraceptive method for women with epilepsy needs broad concerns regarding its effectiveness and drug-drug interaction with AEDs used. The use of IUD is mostly recommended to avoid the metabolism effects of both AEDs and hormonal contraceptives. Never rule out the vital role of counseling in women with epilepsy, the neurologist and gynecologist should explain and discuss this issue more frequently in every visit, to ensure whether the patient understand about how they quality of life be achieved by choosing the right AED and hormonal contraceptive.

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