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The impact of antiepileptic drug therapy on steroidal contraceptive efficacy

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Abstract

Women with epilepsy face unique challenges in maintaining steroidal contraceptive efficacy because some antiepileptic drugs (AEDs) increase the rate of hepatic metabolism of contraceptive steroids, leading to higher potential for contraceptive failure in this population. Planned pregnancy is of great clinical and social importance for women with epilepsy because of the increased risk of birth defects from fetal exposure to AEDs. Current clinical guidelines for contraceptive management in women with epilepsy provide misleading information by focusing on the estrogen content of the formulation, which regulates the menstrual cycle, rather than on the progestin content of the formulation, which provides contraceptive efficacy. This article reviews studies of AED–contraceptive interaction and misconceptions about maintaining contraceptive efficacy and makes recommendations for contraceptive management in women with epilepsy who receive concomitant AED therapy.

Keywords: Antiepileptic drugs; Contraception; Efficacy; Enzyme induction; Epilepsy; Treatment guidelines; Hepatic metabolism; Steroidal contraceptives; Women

1. Introduction

Women with epilepsy who are treated with antiepileptic drugs (AEDs) face unique challenges in contraception. Certain AEDs can induce hepatic metabolism of steroidal contraceptives (SCs), leading to decreased contraceptive efficacy. However, several surveys suggest that a large percentage of health care professionals have limited knowledge about optimizing contraceptive efficacy in female patients with epilepsy [1,2], that women of reproductive age who are treated with enzyme-inducing AEDs do not receive information about potential drug interactions [3], and that women who take AEDs have a high oral contraceptive (OC) failure rate [1].

Although more than 90% of women taking AEDs during pregnancy will deliver a healthy child, 4–7% of fetuses exposed to certain AEDs are at increased risk of having birth defects [4]. Therefore, contraceptive efficacy is a major concern for women with epilepsy. A lack of confidence in the method of contraception can lead to detrimental psychosocial stresses, including decreased sexuality and fear of teratogenesis.[5] Women with epilepsy desire treatment that offers optimal seizure control together with reliable birth control, healthy pregnancies, and healthy children [6]. Good counseling and pregnancy planning are essential to achieving these goals.

This article reviews the published literature addressing AED–contraceptive interaction, discusses misconceptions

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in current contraception management in women with epilepsy, and offers recommendations on reliable contraception methods for women to use concomitantly with AEDs.

2. Current contraception guidelines for women with epilepsy: Flaws

Current guidelines for contraceptive use by women with epilepsy suggest that contraceptive efficacy is provided by the estrogen component of these agents [7,8]. In fact, it is the progestin component of SCs that provides contraceptive efficacy [9,10].

For example, the Commission on Genetics, Pregnancy, and the Child, International League Against Epilepsy, guidelines for the care of women of childbearing age with epilepsy suggest that breakthrough bleeding is a sign of contraceptive failure that is due to low estrogen dosage resulting from possible interaction between AEDs and SCs [7]. The American Academy of Neurology (AAN) Practice Parameters recognize that the risk of contraceptive failure may be increased as endogenously bioavailable estrogen and progestin are reduced by the use of those AEDs that activate isozymes of hepatic cytochrome P450 (CYP450) or increase production of steroid hormone-binding globulins (SHBGs). AAN guidelines recommend that the contraceptive formulation contain at least 50 μg of ethinylestradiol or mestranol to control breakthrough bleeding [8]. Neither set of guidelines makes recommendations for progestin dosage.

Although the available guidelines recognize that some AEDs can reduce the efficacy of SCs, they provide flawed guidance for providing effective contraception. Although estrogen levels are reduced by the action of enzyme-inducing AEDs, it is the progestin component of the contraceptive that prevents ovulation. Current guidelines omit this crucial information.

3. Steroidal contraceptive mechanism of action

During the first stage of the menstrual cycle (follicular phase), the hypothalamus produces gonadotropin-releasing hormone (GnRH). GnRH stimulates the pituitary gland to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH), causing follicles to mature in the ovaries. Pituitary FSH secretion drives the production of estrogen, which gradually increases throughout the follicular phase. Just before ovulation, the negative feedback of estrogen on pituitary LH/FSH changes to positive feedback. This produces a surge in LH, as well as a surge in estradiol, which causes release of the oocyte from the follicle in the ovary into the fallopian tubes (ovulation). In the second stage of the menstrual cycle (luteal phase), the granulosa cell remnants of the follicle form the corpus luteum, which secretes large quantities of progesterone and, to a lesser degree, estradiol in response to LH. These hormones prepare the endometrium for implantation of the fertilized egg. If fertilization does not occur, production of estrogen and progesterone decreases, and menstruation begins [11].

In the 1950s, the initial development of SCs was based on the observation that progesterone is responsible for the suppression of ovulation. In early tests of contraceptives, the use of impure progestogen samples provided evidence that estrogen was necessary for menstrual cycle regulation [12]. Analysis of bleeding patterns in women using a number of contraceptive modalities has confirmed the necessity of estrogen for proper cycle control [13]. Progestin-induced irregular menstruation may provide misleading evidence of altered hormone cycling due to pathology [14]. Therefore, scheduled endometrial shedding brought about by the oral intake of estrogen may contribute to psychological well-being as well as convenience.

Currently, SCs contain either a combination of synthetic estrogen and synthetic progesterone-like steroid or a single synthetic progesterone-like component (Fig. 1) [15]. Typically, the synthetic estrogen component of combined SCs comprises either ethinylestradiol or mestranol. Ethinylestradiol is an orally active derivative of the endogenous hormone estradiol, with the addition of an ethinyl group to the pentane ring. Mestranol is essentially ethinylestradiol with a methylated hydroxyl group on the benzene ring. The progesterone-like component of either combined or single-agent contraceptives comprises one of a variety of synthetic progestational steroids called progestins or progestogens, which are similar in structure to the native hormone progesterone. Norethindrone, for example, differs from progesterone by the lack of a methyl group at position 6 and the substitution of a hydroxyl group and an ethinyl group for the ketone at position 17. Levonorgestrel differs from norethindrone by the substitution of an ethyl group for the methyl group at position 13 [16,17].

Progestins induce four discrete contraceptive processes in the body. First, they inhibit production of GnRH by the hypothalamus. The reduction in GnRH limits production of LH and of FSH by the pituitary gland, thereby suppressing the midcycle pulses of LH necessary to initiate ovulation (Fig. 2) [18]. Second, progestins cause cervical mucus to thicken, which blocks the passage of sperm. Third, they cause the endometrium to atrophy, making it unsuitable for ovum implantation. Fourth, they limit fallopian tube cilial motility, preventing the timely transport of the ovum to the uterus [9,19].

The estrogen component of combined SCs plays two important physiologic roles. First, estrogen augments the effects of progestins by increasing the concentration of intracellular progestin receptors. Estrogen also suppresses the release of FSH from the pituitary, further inhibiting the emergence of a dominant follicle. Therefore, estrogen may contribute indirectly to the efficacy of combined SCs. Second, and more importantly, estrogen stabilizes the endometrium, minimizing breakthrough bleeding and unscheduled endometrial shedding, which increase patient satisfaction and compliance [10].

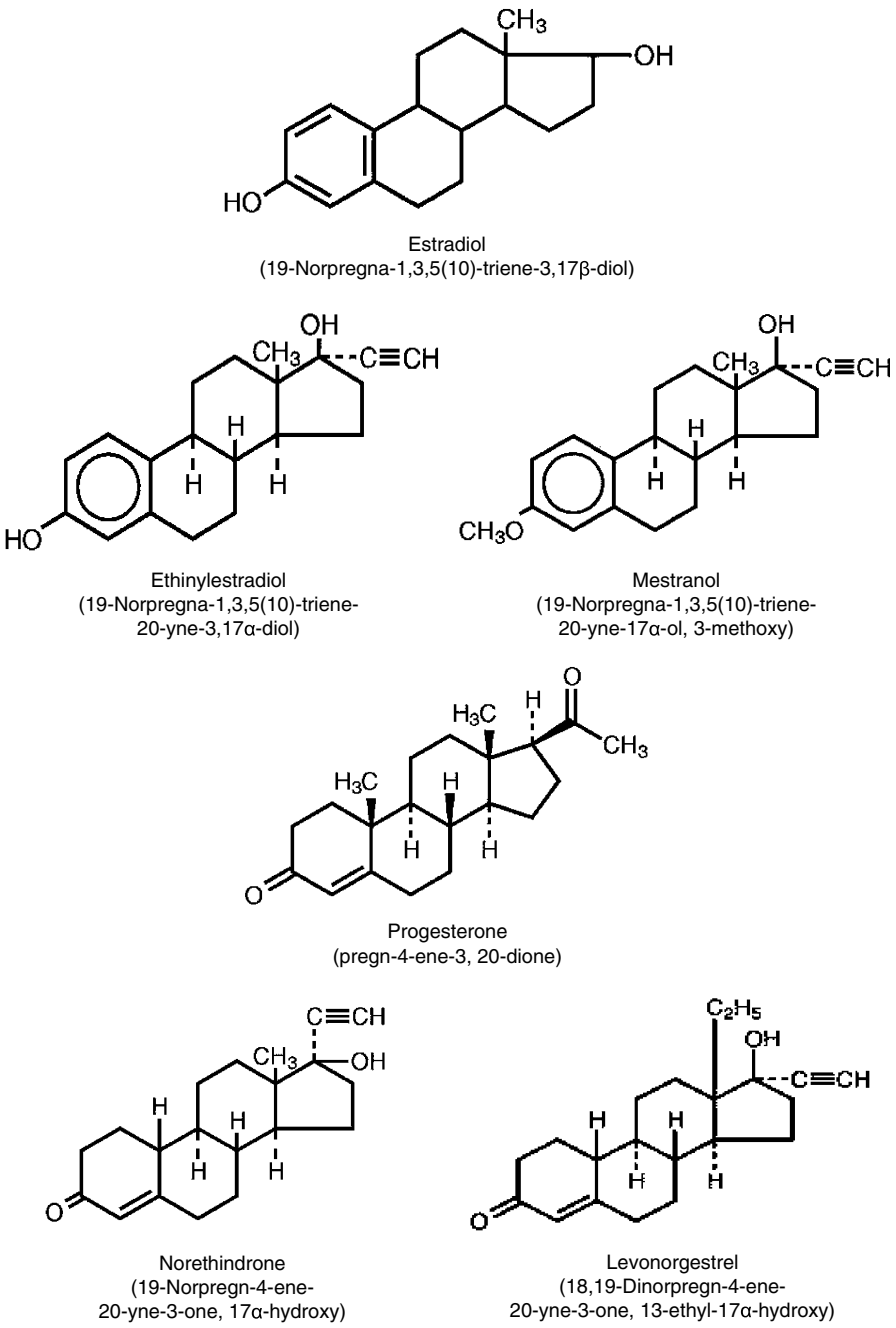

Fig. 1. Chemical structures for gonadal steroids and their synthetic derivatives. Not all progestational agents are represented. Adapted, with permission, from ChemIndustry.com, Monrovia, CA, USA, and Drugs.com, Drugsite Trust, Auckland, New Zealand.

4. Drug interactions between AEDs and steroidal contraceptives

4.1. Impact of AEDs on steroidal contraceptives

Gonadal steroids and their synthetic derivatives are metabolized by hepatic CYP450 enzymes, specifically the CYP3A4 isoform group. These enzymes are induced by a number of drugs, including AEDs such as phenobarbital, phenytoin, and carbamazepine. In addition, gonadal steroids and their synthetic derivatives are carried in the blood largely bound to the carrier protein SHBG, with only the unbound fraction of the steroids being bioactive. SHBG is synthesized by the liver, and its synthesis is stimulated by the enzyme-inducing AEDs. Therefore, enzyme-inducing AEDs lower plasma levels of active SC by increasing the rate of their catabolism and clearance and by increasing the amount of SHBG to which they bind. This can result in contraceptive failure and breakthrough bleeding when serum levels of progestin and estrogen fall below effective concentrations.

Progestins have a bioavailability of between 80 and 100% because they do not undergo significant initial gut or hepatic metabolism. Induction of CYP3A4 by enzyme-

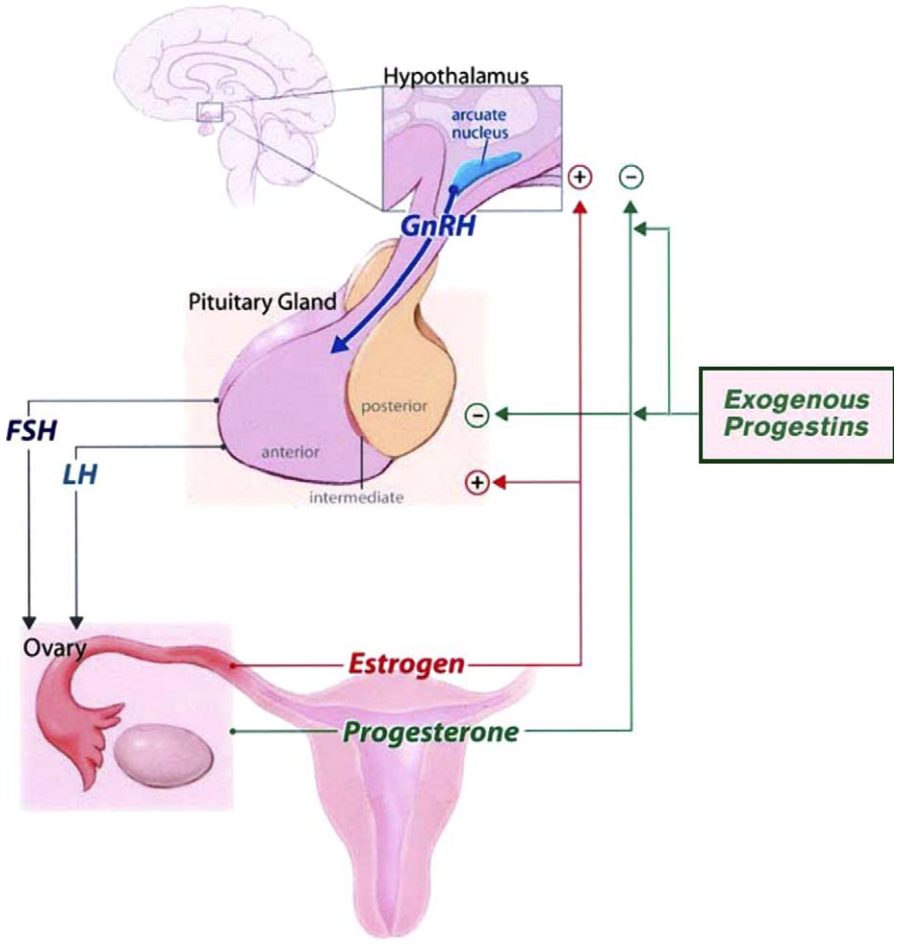

Fig. 2. The progestin component of steroidal contraceptives suppresses ovulation by inhibiting hormone production by the hypothalamus and pituitary gland. Adapted, with permission, from Foldvary-Schaefer N, Falcone T. Catamenial epilepsy: pathophysiology, diagnosis, and management. Neurology 2003;61(6, Suppl. 2):S2–15.

inducing AEDs increases the rate of secondary progestin metabolism [4], resulting in decreased serum concentrations of progestins. By contrast, the bioavailability of ethinylestradiol is generally 40–50% as a result of first-pass metabolism. Ethinylestradiol undergoes sulfation in the intestine and glucuronation or CYP3A4-catalyzed hydroxylation in the liver [4]. Enzyme-inducing AEDs increase secondary metabolism of both estrogens and progestins by inducing CYP3A4. They further reduce free steroid levels by inducing the production of SHBG, which binds these steroids in the blood [20].

4.1.1. Inducers of hepatic enzymes

Several first- and second-generation AEDs have significant enzyme-inducing properties and act on a wide spectrum of hepatic enzymes that metabolize the progestin and estrogen components of SCs (Table 1). Crawford et al. demonstrated that carbamazepine use was associated with a 6–66% reduction in serum ethinylestradiol concentration and a 29–57% reduction in serum levonorgestrel concentration [21]. In a similar study, carbamazepine use was associated with a 58% reduction in serum norethindrone and a 42% reduction in serum ethinylestradiol [22]. Back et al. reported that women taking phenobarbital had decreased serum ethinylestradiol concentrations (64 and 72%), with associated breakthrough bleeding. However, serum FSH and progesterone levels did not change, suggesting ovulation did not occur in these patients [23]. In the absence of information to the contrary, primidone should be considered to have effects on SC metabolism similar to those of phenobarbital. Significant reductions in serum ethinylestradiol (49%) and levonorgestrel (42%) have been observed in concurrent phenytoin and SC use [21].

Of the second generation AEDs, felbamate has been shown to reduce serum gestodene by 42% and to reduce ethinylestradiol by 13%, although there was no evidence of ovulation among these patients [24]. In female volunteers, 300 mg/day doses of lamotrigine decreased levonorgestrel levels by 19%, although there was no evidence of ovulation in these subjects and no apparent effect on ethinylestradiol concentration [25]. Oxcarbazepine at 300 mg/day decreased the serum concentration of ethinylestradiol by 48% and that of levonorgestrel by 32%. However, serum progesterone levels remained low, indicating that ovulation

Table 1
Observed effects of AEDs on steroidal contraceptive metabolism

	Activated enzymes	Estrogen reduction (%)	Progestin reduction (%)
Inducers of hepatic enzymes			
Carbamazepine [22,28] 600 mg/day	CYP1A2, CYP2C, CYP3A	42	58
Felbamate [24,28] 2400 mg/day	CYP3A4	13	42
Lamotrigine [25]	Not reported	—	19
Oxcarbazepine [26,28] 300 mg/day	CYP3A4	48	32
Phenobarbital [23,28] 60 mg/day	CYP1A, CYP2A6, CYP2B, CYP2C, CYP3A	64–72	—
Phenytoin [21,28] 200–300 mg/day	CYP2C, CYP3A	49	42
Topiramate [22,28] 200 mg/day	CYP3A4	14.7–33.0	—
Non-inducers of hepatic enzymes			
Ethosuximide [20,28]	—	—	—
Levetiracetam [28,43]	—	—	—
Tiagabine [4,28]	—	—	—
Valproic acid [28,44]	—	—	—
Vigabatrin [28,45]	—	—	—
Zonisamide [28,46]	—	—	—

did not occur in these patients [26]. In doses of 100–400 mg/day, topiramate has been shown to decrease serum ethinylestradiol levels by ⩽30%, but topiramate had no significant effect on norethindrone concentrations [27]. However, a separate study of topiramate at ⩽200 mg/day indicated no significant effect on ethinylestradiol or norethindrone serum levels [22].

4.2. Non-inducers of hepatic enzymes

~~Many~~ first- and second-generation AEDs are not potent inducers of hepatic enzymes. They may be less active, may activate through less important enzyme pathways, or may have no effect whatsoever. Ethosuximide, gabapentin, levetiracetam, tiagabine, valproic acid, vigabatrin, and zonisamide have no appreciable enzyme-inducing action and appear not to compromise SC efficacy [28].

4.3. Impact of steroidal contraceptives on AEDs

SCs may impact the serum concentration and efficacy of certain AEDs, most notably lamotrigine. In case studies, SCs decreased the serum level of lamotrigine by a mean 49% (range: 41–64%). In these patients, seizure activity increased with SC use, and the side effects of lamotrigine increased when SCs were discontinued [29]. In a pilot study of SC impact on serum lamotrigine levels, 22 women received lamotrigine and an SC, and 30 women received lamotrigine alone. Serum lamotrigine decreased by more than 50% in the women taking lamotrigine and SCs concurrently [30]. These studies suggest that the pharmacokinetics of lamotrigine are significantly altered by SC use. SCs induce UDP-glucuronosyltransferase (UGT), the primary pathway of lamotrigine elimination [30]. Therefore, dose adjustments should be considered~~,~~ to compensate for the marked reductions in lamotrigine that are associated with elevated serum estrogen and progestin. Serum steroid levels rise in pregnancy, with a similar drop in lamotrigine levels, followed by rise in the lamotrigine level in the postpartum period. Lamotrigine dose adjustments should be considered in both patient populations to ensure maximum seizure suppression. Further studies of the effects of SC use on AEDs are needed so that guidelines for dose adjustments during SC initiation and withdrawal can be developed.

4.4. Summary

The induction of CYP450 isozymes by many AEDs increases the metabolism of SCs, which potentially compromises contraceptive efficacy. Carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, and topiramate have been shown to significantly reduce serum concentrations of SCs, whereas ethosuximide, gabapentin, levetiracetam, tiagabine, valproic acid, vigabatrin, and zonisamide appear not to induce CYP450. Conversely, SCs may impact AED efficacy because SCs induce UGT activity. Serum levels of lamotrigine, in particular, may be significantly reduced in women who also use SCs.

The potential for drug interactions between AEDs and SCs appears to be high. However, the available studies on concurrent AED and SC use have been conducted in small numbers of patients. These results need to be confirmed in larger, well-designed, prospective clinical trials. In particular, serum concentrations of SCs need to be correlated with contraceptive failure rates so that clear guidelines for the clinical management of drug interactions between AEDs and SCs can be developed.

5. Non-oral contraceptives

Women who use enzyme-inducing AEDs and SCs concomitantly have a higher rate of contraceptive failure than the general population [31–33]. Administering higher-dose SCs could reduce the risk of contraceptive failure by accommodating the increased steroid metabolism caused by enzyme-inducing AEDs. For women who need alterna-

tives to OCs, intrauterine devices and injectable contraceptives appear to be the best candidates because they have not exhibited high susceptibility to enzyme-inducing AEDs [20]. Therefore, alternative contraceptives may help decrease the rate of contraceptive failure in women with epilepsy.

5.1. Intrauterine contraceptives

In 2000, the U.S. Food and Drug Administration (FDA) approved the use of Mirena, a levonorgestrel-releasing intrauterine system (LNG-IUS). The LNG-IUS initially delivers 20 μg/day levonorgestrel and remains effective for approximately 5 years [34]. Because the LNG-IUS releases hormones locally in the uterus, the potential for drug interaction through enzyme induction is low. In a pilot study of LNG-IUS, compared with a contraceptive failure rate of 0.2/100 woman-years for women not receiving AED treatment, the rate for women receiving concurrent AED treatment was 1.1/100 woman-years, which is less than the failure rate in women using OCs in combination with enzyme inducing AED treatment [35]. The observed difference in efficacy for women receiving AED treatment is perhaps due to peripheral absorption of levonorgestrel from the intrauterine device, which may decrease the viscosity of cervical mucus. Given the contraceptive efficacy of LNG-IUS, it may prove to be a first-line contraceptive method for women who are receiving enzyme-inducing AEDs. Paraguard is an alternative, copper intrauterine device. It provides highly effective contraception because copper has spermicidal properties and local effects that prevent implantation [36]. Because the copper device is not affected by steroid metabolism, it is a good contraceptive method for women receiving enzyme-inducing AEDs.

5.2. Injection contraceptives

In 1992, the FDA approved Depo-Provera, an injection formulation of depomedroxyprogesterone acetate (DMPA). Worldwide, approximately 8–9 million women use this method of contraception [9]. DMPA is a progestin-only agent that is administered via intramuscular injection every 3 months and delivers 150 mg of medroxyprogesterone acetate [37]. Pilot studies of DMPA suggest that drug interactions due to enzyme induction are negligible [38]. In addition, DMPA may have an anticonvulsant effect. In a study of women with medically refractory partial seizures and normal ovulation cycles, treatment with 150 mg of depomedroxyprogesterone resulted in a 40% average reduction in seizures [39]. The anticonvulsant effect may be secondary to DMPA amenorrhea. DMPA appears to be an attractive contraceptive method for women receiving AED treatment, especially for women who may be noncompliant or cognitively impaired and for those for whom estrogen use is contraindicated [18]. A new formulation of DMPA, Depo-SubQ Provera 10, has been approved by the FDA. The new formulation delivers 104 mg medroxyprogesterone acetate and is administered every 3 months [40]. However, this low-dose formulation should not be used in patients receiving enzyme-inducing AEDs because its efficacy may be compromised by increased rates of steroid metabolism.

5.3. Transdermal contraceptives

Ortho Evr is the first contraceptive patch to be approved by the FDA. It delivers 150 μg of norelgestromin and 20 μg of ethinylestradiol daily. A new patch is applied each week for 3 consecutive weeks, followed by a patch-free week that allows menstruation [41]. However, the risk of contraceptive failure in female patients with a body mass index $>27.3\ kg/m^2$ is increased compared with that of women with a smaller volume of distribution [42]. Therefore, it is possible that the relatively low-progestin-dose contraceptive patch might also be less effective in women receiving enzyme-inducing AEDs because of the resultant increased metabolism of the SC. More studies specific to this form of SC are needed to further delineate potential interactions between these two classes of drugs.

5.4. Summary

Although efficacy data for alternative SCs in women receiving AED treatment are limited, their methods of delivery may offer clinical benefits, including a lesser degree of drug interaction and improved patient compliance. Transdermal contraceptives deliver low doses of progestin and should not be used by women receiving enzyme-inducing AEDs. LGN-IUS and intramuscular DMPA appear to be attractive contraceptive choices for women receiving enzyme-inducing AEDs. Pilot studies show promise for these agents, with potential for lower rates of contraceptive failure in women with epilepsy. The possible anticonvulsant effect of DMPA may be an additional advantage. However, the efficacy studies to date have included only small numbers of patients. Well-designed, prospective studies need to be conducted to determine the utility of these methods in women who are receiving concurrent AED treatment.

6. Treatment recommendations

Enzyme-inducing AEDs have the potential to compromise the efficacy of all SCs. Conversely, lamotrigine may also compromise the efficacy of AEDs. Given how the frequency and severity of seizures impact women's lives, epilepsy must be the treatment priority. Therefore, the most effective AED should be used to treat each type of epilepsy, while considering the potential effects of the AED on the patient's SC metabolism and making adjustments to ensure efficacy. At the same time, women who are considering alternative methods of steroidal contraception should be advised of the risks or benefits of these agents.

Table 2
Estimates of bioavailable steroid after hepatic metabolism

Steroid	Dose	Bioavailable steroid			Minimally effective dose
		After 25% metabolism	After 50% metabolism	After 65% metabolism	
Norethindrone	1 mg	0.75 mg	0.5 mg	0.35 mg	0.35 mg
Levonorgestrel	0.150 mg	0.113 mg	0.075 mg	0.053 mg	0.0375 mg
Levonorgestrel	0.250 mg	0.188 mg	0.125 mg	0.0875 mg	0.0375 mg
Ethinylestradiol	35 μg	26.5 μg	17.5 μg	12.25 μg	20 μg
Ethinylestradiol	50 μg	37.5 μg	25 μg	17.5 μg	20 μg

6.1. Oral contraceptives

Table 2 illustrates the various amounts of ethinylestradiol, norethindrone, and levonorgestrel one would expect to be remaining if the administered dose had been metabolized 25, 50, and 65%. For comparison, the last column in Table 2 lists the minimum effective amounts of progestin in FDA-approved progestin-only OCs. In combined OCs containing 50 μg of mestranol as the estrogen component, in vivo metabolism of this prodrug yields approximately 35 μg of bioavailable ethinylestradiol.

For example, in a patient treated with carbamazepine who was also using a combined OC containing 1 mg of norethindrone and 50 μg of ethinylestradiol, the progestin component of her OC could be reduced by 58%, and the estrogen component could be reduced by 42% (Table 1). Because the expected 58% decrease in progestin would not reduce the dose to less than the minimally effective dose of 0.35 mg available as a minipill, an OC containing 1 mg of norethindrone should be an effective contraceptive in this patient. Although the bioavailable ethinylestradiol from this combined OC would potentially be reduced by 42%, the patient would still receive a higher dose than the 20 μg in combined OCs containing lower doses of estrogen.

Tables 3A,3B lists recommended SCs and notes dosages of estrogen and progestin. Given the rates of metabolic reduction for estrogen and progestin following AED interaction, biphasic and triphasic OCs are not recommended because the low first-phase dose of progestin could compromise contraceptive efficacy. Similarly, all progestin-only OCs would be rendered ineffective and should be eliminated from use by individuals using enzyme-inducing AEDs.

Recommended OCs for women receiving AED treatment include those with 1 mg of norethindrone, 0.150 mg of levonorgestrel, or 0.300 mg norgestrel. All oral formulations containing 50 μg of estrogen are recommended, as

Table 3A
Contraceptives recommended for women receiving AED treatment

Registered brand name	Estrogen	Daily dose (μg)	Progestin	Daily dose (mg)
Monophasic OCs [47]				
Ovcon 50	EE	50	NET	1
Ortho-Novum 1/50	Mestranol	50	NET	1
Norinyl 1 + 50	Mestranol	50	NET	1
Ogestrel[a]	EE	50	Norgestrel	0.5
Ortho-Novum 1/35	EE	35	NET	1
Norinyl 1 + 35	EE	35	NET	1
Loestrin 1.5/30	EE	30	NET	1.5
Loestrin Fe 1.5/30	EE	30	NET	1.5
Lo/Ovral	EE	30	Norgestrel	0.3
Nordette	EE	30	LNG	0.15
Loestrin 1/20	EE	20	NET	1
Loestrin Fe 1/20	EE	20	NET	1
Extended-cycle OCs [47]				
Seasonale	EE	30	LNG	0.15
Intrauterine contraceptives [34,36]				
Mirena			LNG	0.20
Paraguard			Copper	
Injection contraceptives [37]				
Depo-Provera (administered quarterly)			MPA	150

[a] Generic name. EE, ethinylestradiol; LNG, levonorgestrel; MPA, medroxyprogesterone acetate; NET, norethindrone.

Table 3B
Contraceptives NOT recommended for women receiving AED treatment[a]

Registered brand name	Estrogen	Daily dose (μg)	Progestin	Daily dose (mg)
Biphasic OCs [47]				
Ortho-Novum 10/11–28	EE	35 (Days 1–10) 35 (Days 11–28)	NET	0.5 (Days 1–10) 1.0 (Days 11–28)
Triphasic OCs [47]				
Tri-Norinyl	EE	35	NET	0.5 (Week 1) 1.0 (Week 2) 0.5 (Week 3)
Progestin-only OCs [47]				
Nor-QD			NET	0.35
Ortho Micronor			NET	0.35
Ovrette			Norgestrel	0.075

[a] Not a comprehensive list. EE, ethinylestradiol; LNG, levonorgestrel; MPA, medroxyprogesterone acetate; NET, norethindrone.

these contraceptives also contain relatively high doses of progestin. Therefore, patients receiving combined OCs containing 50 μg of estrogen should have effective contraception and adequate menstruation cycle control.

6.2. Non-oral contraceptives

The contraceptive patch should not be used by women receiving AED treatment because it is a low-progestin-dose method [38]. The 150-mg preparation of DMPA may be an effective contraceptive option for women with epilepsy because it appears to have little or no drug interaction with AEDs. Likewise, the LNG-IUS may be an effective alternative for women receiving AED treatment because the localized, intrauterine delivery of steroids appears to be unaffected by AED-induced enzyme metabolism. DMPA injections and LNG-IUS appear to have better efficacy than OCs and barrier methods, but studies to date are based on small numbers of patients. The efficacy of these alternative SCs needs to be further studied in women with epilepsy.

7. Conclusion

The concern about the increased risk of teratogenicity of certain AEDs makes planned pregnancy of greater concern for women with epilepsy than for women in the general population. The available guidelines for steroidal contraception for women with epilepsy focus misguidedly on the estrogen component of combined SCs, which helps to regulate menstrual cycles, rather than the progestin component, which suppresses ovulation and is responsible for contraception efficacy. Low-dose SC use by women treated with enzyme-inducing AEDs may result in contraceptive failure because induction of the CYP450 enzymes responsible for steroid metabolism increases clearance and reduces plasma SCs to levels insufficient for ovulation suppression. Conversely, SCs can impact the serum concentration of AEDs by inducing UGT activity. Lamotrigine, in particular, appears to be susceptible to increased clearance through SC use.

Given the potential for drug interactions between SCs and AEDs, we recommend combined OCs with relatively high progestin doses to ensure contraceptive efficacy. For women who seek alternatives to OCs, intrauterine devices and injection contraceptives are effective and appear to have less potential for drug interaction than OCs. However, well-designed, prospective trials are needed before clear guidelines on the administration of AEDs and SCs can emerge.

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