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FAMILY PLANNING (A BURKE, SECTION EDITOR)

Contraception for Women with Epilepsy

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Abstract

Purpose of Review The purpose of this review is to summarize the current available literature on contraception for women with epilepsy, and to provide recommendations for women with epilepsy on enzyme-inducing anti-seizure drugs and on non-enzyme-inducing anti-seizure drugs.

Recent Findings A recent study has confirmed the safety of the levonorgestrel-containing intrauterine device for women with epilepsy, with no effect on seizure control or anti-seizure drug levels. Other recent studies have found low serum etonogestrel or levonorgestrel levels in women on enzyme-inducing anti-seizure drugs and the etonogestrel or levonorgestrel implant, making this an unsuitable method for women on such drugs.

Summary Women with epilepsy have an especially compelling need to avoid unplanned pregnancy, as some common anti-seizure medications have teratogenic or detrimental neurocognitive effects on exposed children. Women on enzyme-inducing anti-seizure drugs and their physicians must be particularly aware of drug interactions with hormonal contraceptive methods.

Keywords Epilepsy and contraception · Anti-seizure drugs · Anti-epileptic drugs · Epilepsy and women

Introduction

Pregnancy planning and effective contraception are of vital importance for women with epilepsy (WWE). Many anti-seizure drugs (ASDs) used to control epileptic seizures have the potential for teratogenic effects, low birth weight, and neurocognitive effects in offspring exposed to the ASDs in utero [1, 2•, 3]. Generalized tonic-clonic seizures during pregnancy are associated with prematurity and low birth weight [4]. Therefore, effective contraception so that pregnancy can be avoided until desired is a high concern for WWE (Box 1).

Box 1 Highly effective means of contraception of choice for patients on EI-ASDs

Intrauterine device – copper
Intrauterine device – levonorgestrel
Depot medroxyprogesterone acetate (DMPA)
Tubal ligation

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While WWE are in need of effective contraception, they also have unique challenges. Many ASDs interact with hormonal contraception, reducing the effectiveness of contraception or of the ASD, which can lead to unintended pregnancies or breakthrough seizures. In addition, some exogenous hormones can have an effect on seizures, raising the possibility that seizure control may be affected by contraception itself.

Hormonal Aspects of Epilepsy

Epilepsy is a disorder characterized by recurrent, unprovoked seizures [5]. Epileptic seizures are symptoms or signs caused by abnormal firing of neurons in the brain [6], and consist of generalized body shaking, sudden loss of awareness, confusion, abnormal limb movements, or other symptoms. First-line therapy for seizures involves medication with ASDs, which can control seizures in approximately 2/3 of patients with epilepsy [7].

About 1/3 of women have an increase in seizures related to the menstrual cycle. This seizure exacerbation can occur in the premenstrual phase, around the time of ovulation, or throughout the luteal phase in anovulatory cycles [8]. Experiments in the 1950s demonstrated that exogenous estrogen produces an increase in epileptiform brain activity in WWE [9], while progesterone (and in particular the naturally occurring metabolite

allopregnanolone) has a calming effect on epileptiform brain activity [10, 11].

AED-Hormonal Contraceptive Interactions

Effect of ASDs on Contraceptives

The effects of ASDs on oral contraceptives, including contraceptive failure resulting in failure and breakthrough bleeding, have been known since the 1970s [12]. Many ASDs, particularly earlier ASDs such as carbamazepine and phenytoin which were approved before 1990, have enzyme-inducing effects on liver enzymes. These enzyme-inducing ASDs (EI-ASDs) particularly affect the cytochrome P450 and glycuronyl transferase systems [13]. Estrogens (and progestins) are metabolized in part by the cytochrome P450 [14•]. In addition, EI-ASDs can increase sex hormone–binding globulin. Together, these effects can lead to decreased serum estrogen levels, for both physiologic and exogenous estrogen compounds. In women not taking hormonal birth control, this can lead to menstrual irregularities [15, 16] and to sexual dysfunction [17]. In women taking an estrogen-containing birth control, the exogenous estrogen is effectively lowered, which can lead to breakthrough ovulation and decreased effectiveness of birth control. Table 1 lists common ASDs and their effects on estrogen and progesterone.

Multiple studies have demonstrated the interactions between contraceptives and ASDs. Therefore, the World Health Organization Working Group on medical eligibility for contraceptive use has recommended that women taking EI-ASDs do not use COCs, progesterone-only pills, transdermal patch, or vaginal ring as first-line contraceptive therapy due to the risk of unintended pregnancy [30]; US Medical Eligibility for Contraception (MEC) guidelines are similar, encouraging women on EI-ASDs to use alternatives to these methods [31]. Women on EI-ASDs should be encouraged to use one of the highly effective methods in Table 2 [31].

Oral Contraceptives

EI-ASDs reduce ethinyl estradiol levels from COC, and thus low-dose COC are not advisable in women taking these medications. Women who must take an EI-ASD and COC should take a preparation with at least 30–50mcg/day of estrogen [31, 32].

One study of ten women who completed a crossover study of low-dose (20 μg ethinyl estradiol and 100 μg levonorgestrel) COC and carbamazepine use found that ovulation occurred in five of ten women on carbamazepine versus one of ten on placebo, and 3 or more days of breakthrough bleeding occurred in eight of ten women on carbamazepine compared to two of ten on placebo; ethinyl estradiol and levonorgestrel levels were significantly lower during carbamazepine use [33]. A related ASD, oxcarbazepine, also reduced estrogen and levonorgestrel levels by 47% in 22 women taking COC and oxcarbazepine, compared to COC and placebo [34]. The newest related medication, eslicarbazepine, also decreased ethinyl estradiol exposure by up to 42% in a crossover trial of 20 healthy women [19]. These reductions are predicted to be clinically significant (i.e., could lead to breakthrough ovulation and failure of contraceptive efficacy) as they are similar

Table 1 Common anti-seizure drugs (ASDs) and their effects on estrogens and progestins

ASD	Effect on estrogens by ASD (% reduction, where available)	Effect on progestins by ASD (% reduction, where available)
Enzyme-inducing ASDs		
Carbamazepine	Reduced (43) [18]	Reduced (40) [18]
Eslicarbazepine	Reduced (42) [19]	Reduced (24) [19]
Oxcarbazepine	Reduced (47) [20]	Reduced (47) [20]
Phenobarbital	Reduced (50) [21]	Reduced [22]
Phenytoin	Reduced (50) [18]	Reduced (42) [18]
Topiramate	Reduced (30; at ≥ 200 mg/day) [20]	No effect [23]
Perampanel	No effect [20]	Reduced (40; at ≥ 12 mg/day) [20]
Non-enzyme-inducing ASDs		
Gabapentin	No effect [24]	No effect [24]
Lacosamide	No effect [25]	No effect [25]
Levetiracetam	No effect [26]	No effect [26]
Lamotrigine	No effect (reduced by estrogen) [27]	Reduced (19) [27]
Valproate	No effect [28]	No effect [28]
Zonisamide	No effect [29]	No effect [29]

to the reductions in carbamazepine which led to breakthrough ovulation [33, 34].

In women who add phenytoin to a standard-dose COC, ethinyl estradiol levels are reduced by 50% compared to baseline [18]. Topiramate reduces ethinyl estradiol steady-state levels by up to 30%, with a dose-dependent effect [23]. Similarly, phenobarbital lowers the level of ethinyl estradiol by over 50% compared to baseline and can cause breakthrough bleeding in women taking oral estrogen preparations [21]. Perampanel, a newer ASD, reduces levonorgestrel by 40% [20].

Similarly, progesterone-only pills (POPs) rely on sufficient serum levels of progesterone, and as the level of progesterone is decreased by EI-ASDs, POPs are not recommended for contraception in women taking EI-ASDs [35]. However, pharmacokinetic and pharmacodynamics studies are lacking.

Many newer ASDs do not have enzyme-inducing properties and therefore do not interact with COCs or POPs. Levetiracetam, one of the most commonly prescribed ASDs to women of childbearing age [36], had no effect on levonorgestrel or ethinyl estradiol levels (or progesterone or luteinizing hormone levels) in a study of 18 women taking levetiracetam and COC (30 mcg ethinyl estradiol and 150 mcg levonorgestrel) [26]. Lamotrigine, also commonly used in young women [36], does not reduce serum levels of ethinyl estradiol. Serum levels of progestins may be somewhat reduced by lamotrigine; however, ovulation remained suppressed in a study of 16 women on lamotrigine and COCs (with 30 mcg ethinyl estradiol and 150 mcg levonorgestrel) [27]. A study of lacosamide and low-dose COC use in 31 women found no difference in ethinyl estradiol and levonorgestrel levels or incidence of ovulation between months in which COC was taken alone, and months in which lacosamide was taken with the COC [25]. Zonisamide had no effect on ethinyl estradiol or progestin levels in a study of 37 healthy women [29]. For these non-EI-ASDs, there is no need to avoid or adjust the dose of COCs for contraceptive efficacy.

Valproate does not affect serum ethinyl estradiol or levonorgestrel levels [28], however has a higher risk of teratogenicity [1] and should not be first-line therapy for women of childbearing potential when alternatives exist.

Intrauterine Devices

The intrauterine device (IUD) is a safe and highly effective method of contraception for women with epilepsy, and is highly recommended for this population [37]. Studies have found that IUD use is reported by 17–18% of women with epilepsy at risk of becoming pregnant [38, 39], perhaps as a result of counseling by physicians who encourage the IUD in WWE [40]. The copper IUD, used by 5% of women with epilepsy [38], does not rely on hormones, and therefore may be used effectively by women taking all types of ASDs. Progestin IUDs are used by 12% of women with epilepsy [38]. As it does not contain estrogen, the major interactions listed above for COCs are not relevant; serum progesterins may be mildly decreased (see Table 1). However, the progestin IUD relies on local progestin effects, and therefore it is also considered safe and effective for women with epilepsy taking EI-ASDs [40]. One observational series of 56 women taking enzyme-inducing drugs and using a progestin IUD found that in a combined 1075 months at risk for pregnancy, there was only one reported pregnancy (a failure rate of 1.1 per 100 woman-years) [41].

Implants

One study of the etonogestrel implant (Nexplanon) found that in ten healthy women using an etonorgestrel implant for 1–3 years (median 23 months) who took carbamazepine (600 mg/day), etonogestrel concentrations decreased by a median of 61% (range 25–87%). Eight of the ten women had etonogestrel concentrations below 90 pg/mL, the concentration at which ovulation is thought to be prevented, suggesting a high risk for contraceptive failure [42]. Similarly, an older study found that levonorgestrel implant (Norplant) users taking EI-ASDs had 38% lower serum levels of levonorgestrel, and unintended pregnancies occurred in two of nine women with epilepsy (22%) on EI-ASDs followed for 1 year [43]. Other studies on implants are lacking. Therefore, progestin implants are not considered reliable in women on EI-ASDs (though may be used by women on non-EI-ASDs).

Depot Medroxyprogesterone Acetate

The depot medroxyprogesterone acetate (DMPA) is a progestin administered via injection that relies on sufficient serum levels of progesterone. The clearance of DMPA is largely equal to hepatic blood flow, suggesting that inducing agents will not significantly affect the metabolism [20, 32, 44]. The current recommendation if DMPA is used is to administer without adjusting the dose or injection interval [31]. However, observational studies are lacking. As discussed below, in women with amenorrhea following DMPA administration, there are reports of improvement in seizure frequency [45].

Natural Family Planning/Fertility Awareness–Based Methods

While not considered highly effective, some women use natural family planning/fertility awareness methods as birth control. Due to increased sex hormone–binding globulin caused by some EI-ASDs, menstrual cycles may be less predictable in women taking those EI-ASDs [15, 16], which could make

fertility awareness–based methods less reliable in women on EI-ASDs. However, observational studies are lacking.

Barrier Methods

Barrier methods including male condom and diaphragm are reported by 39% of women with epilepsy [38], and are safe for all WWE. However, barrier methods are not considered highly effective for women with or without epilepsy [31].

Tubal Ligation

Tubal ligation is reported by approximately in 4% of women with epilepsy of reproductive age, and is safe and highly effective for women on all types of ASDs [38]. While this rate is lower than that of women in the general population, current methods of surveying self-reporting women with epilepsy at risk for pregnancy may not capture women who have already had a tubal ligation [38].

Emergency Contraception

There are no currently available studies of the effects of ASDs on the effectiveness of emergency contraception. As most emergency contraception relies on high doses of progestins to prevent ovulation [46], there is a risk that it will be less effective in women taking EI-ASDs, and a higher dose of 1.5 mg levonorgestrel for the first dose of progestin is recommended [32, 47]. However, there are no studies of emergency contraception in WWE, and no data is available on ulipristal in WWE.

Effect of Hormonal Contraception on ASD Levels

Conversely, hormonal contraceptives can also have an effect on ASD levels. Lamotrigine is metabolized by uridine diphosphate (UDP) glucuronosyltransferase (UGT)–mediated glucuronidation. UGT is induced by ethinyl estradiol, and therefore estrogen increases the metabolism of lamotrigine, effectively decreasing serum lamotrigine levels by 50% or more [48]. This commonly leads to breakthrough seizures or even status epilepticus in women on lamotrigine who start taking a combined oral contraceptive (COC) if the lamotrigine level is not adjusted. In women taking lamotrigine who plan to start COC, a baseline level should be checked prior to start of COC, then lamotrigine dose increased by 25–50 mg per week to at least 150% of the baseline dose, and the COC added when the woman has been on the new dose of lamotrigine for at least 1 week. Similarly, when stopping a COC, the dose of lamotrigine should be lowered to compensate. During the placebo week common to most COCs, the lamotrigine level can increase up to 54% higher than during the active pill week [49]. Some women may be sensitive to lamotrigine side effects during the placebo week. In these cases, a decreased dose of lamotrigine (generally the dose tolerated before COCs were started, if known) during the week without estrogen may be necessary. Progestins do not change the metabolism of lamotrigine, and POPs may be used without dose adjustment of lamotrigine [50].

Similarly, valproate is also metabolized via glucuronidation, and (though not as well characterized) the level can be lowered by up to 23% during active-week COC therapy in a study of 12 women taking valproate and COCs [51]. Due to the high risks of valproate in pregnancy (on both major congenital malformations [1] and neurodevelopment [3, 52]), valproate should not be first-line therapy for women with epilepsy, and alternative medications should be sought. If valproate must be used, more highly effective contraceptives should be encouraged such as the IUD; if this is not feasible, dual use (i.e., of condoms and COCs) should be practiced.

The effects of hormonal contraception on ASDs do not extend to the progestin IUD. A recent prospective study of WWE on ASDs having a progestin-containing IUD placed found no substantial changes in ASD concentrations after placement [53•]. This included women taking lamotrigine, levetiracetam, oxcarbazepine, carbamazepine, lacosamide, valproate, and clobazam. Levonorgestrel levels have not yet been published.

Seizure Control

Case studies have reported improved seizure control in women starting progestin-containing implants, COC, and DMPA [45, 54, 55], while other studies have shown concern for increased seizures in women taking COC [56, 57]. The reason for these different reactions could be related to ASD regimen or COC dose; the lack of individual-level detail from some studies makes comparisons difficult.

For women who experience an improvement in seizure frequency when taking hormonal contraception, induction of amenorrhea and/or the cessation of endogenous estrogen fluctuation (which can lead to seizure exacerbations) are possible mechanisms for the improvement in seizure frequency.

Possible causes for worsened seizure frequency after starting a hormonal contraceptive are the effects on ASD levels (lamotrigine and valproate) as described above, if the ASD doses are not adjusted to compensate. Additionally, the addition of exogenous estrogen may increase neuronal excitation, triggering seizures in susceptible women as has been observed in women starting hormone replacement therapy [58].

Studies

In a recent prospective study of WWE undergoing placement of a progestin-containing IUD, there was no consistent effect on seizure control (three of 20 women reported increased seizures but had stable ASD levels, while four of 20 women reported improved seizure control, also with stable ASD levels) [53•].

DMPA causes cessation of ovulation and amenorrhea in many women. In a small series of 14 women with epilepsy, seven of the 11 who developed amenorrhea reported a 39% decrease in frequency of seizures [45]. As synthetic progestins are not metabolized to allopregnanolone, this is thought to be due to control of endogenous sex hormone fluctuations rather than to neuroprotective properties of DMPA [37].

Conclusions

Pregnancy planning is of special importance for women with epilepsy due to the teratogenicity and long-term neurocognitive effects of some anti-seizure drugs (ASDs). However, enzyme-inducing anti-seizure drugs (EI-ASDs) frequently lower the serum levels of hormonal contraception such as the combined oral contraceptive pill, patch, and progesterone-only pill. For women on EI-ASDs, highly effective reversible contraception of choice includes the intrauterine device (IUD; copper or levonorgestrel-containing) and depot medroxyprogesterone. Estrogen can also lower the serum concentration of lamotrigine, so when initiating a hormonal contraceptive in patients on lamotrigine, the dose must be adjusted accordingly.

Compliance with Ethics Standard

Conflict of Interest Emily L. Johnson declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Hernandez-Diaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, et al. Comparative safety of antiepileptic drugs during pregnancy. Neurology. 2012;78(21):1692–9. https://doi.org/10.1212/WNL.0b013e3182574f39.
2. • Hernández-Díaz S, McElrath TF, Pennell PB, Hauser WA, Yerby M, Holmes LB. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. Ann Neurol. 2017;82(3):457–65. https://doi.org/10.1002/ana.25031 **Prospective study of birth/delivery outcomes in pregnant women with epilepsy.**
3. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013;12(3):244–52. https://doi.org/10.1016/S1474-4422(12)70323-X.
4. Rauchenzauner M, Ehrensberger M, Prieschl M, Kapelari K, Bergmann M, Walser G, et al. Generalized tonic–clonic seizures and antiepileptic drugs during pregnancy—a matter of importance for the baby? J Neurol. 2013;260(2):484–8. https://doi.org/10.1007/s00415-012-6662-8.
5. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82. https://doi.org/10.1111/epi.12550.
6. Fisher RS, Boas W van E, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470–2. https://doi.org/10.1111/j.0013-9580.2005.66104.x.
7. Brodie MJ, Barry SJ, G a B, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology. 2012;78(20):1548–54. https://doi.org/10.1212/WNL.0b013e3182563b19.
8. Herzog AG. Catamenial epilepsy: update on prevalence, pathophysiology and treatment from the findings of the NIH Progesterone Treatment Trial. Seizure. 2015;28:18–25. https://doi.org/10.1016/j.seizure.2015.02.024.
9. Logothetis J, Harner R, Morrell F, Torres F. The role of estrogens in catamenial exacerbation of epilepsy. Neurology. 1959;9(5):352–60 http://www.ncbi.nlm.nih.gov/pubmed/13657294. Accessed 4 Nov 2016.
10. Bäckström T, Zetterlund B, Blom S, Romano M. Effects of intravenous progesterone infusions on the epileptic discharge frequency in women with partial epilepsy. Acta Neurol Scand. 1984;69(4):240–8 http://www.ncbi.nlm.nih.gov/pubmed/6430018. Accessed 4 Nov 2016.
11. Reddy DS. Neuroendocrine aspects of catamenial epilepsy. Horm Behav. 2013;63(2):254–66. https://doi.org/10.1016/j.yhbeh.2012.04.016.
12. Lewis JR. Oral contraceptive and antiepileptic drug interactions resulting in contraceptive failure. JAMA. 1979;241(25):2743. https://doi.org/10.1001/jama.1979.03290510051032.
13. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol. 2006;61(3):246–55. https://doi.org/10.1111/j.1365-2125.2005.02529.x.
14. • Reimers A, Brodtkorb E, Sabers A. Interactions between hormonal contraception and antiepileptic drugs: clinical and mechanistic considerations. Seizure. 2015;28:66–70. https://doi.org/10.1016/j.seizure.2015.03.006 **Good review of relevant interactions.**
15. Isojärvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllylä VV. Menstrual disorders in women with epilepsy receiving carbamazepine. Epilepsia. 1995;36(7):676–81 http://www.ncbi.nlm.nih.gov/pubmed/7555984. Accessed 24 June 2018.
16. Sidhu HS, Srinivasa R, Sadhotra A. Evaluate the effects of antiepileptic drugs on reproductive endocrine system in newly diagnosed female epileptic patients receiving either valproate or lamotrigine monotherapy: a prospective study. Epilepsy Res. 2018;139:20–7. https://doi.org/10.1016/j.eplepsyres.2017.10.016.
17. Luef G, Madersbacher H. Sexual dysfunction in patients with epilepsy. Handb Clin Neurol. 2015;130:383–94. https://doi.org/10.1016/B978-0-444-63247-0.00022-5.
18. Crawford P, Chadwick DJ, Martin C, Tjia J, Back DJ, Orme M. The interaction of phenytoin and carbamazepine with combined oral

contraceptive steroids. Br J Clin Pharmacol. 1990;30(6):892–6. https://doi.org/10.1111/j.1365-2125.1990.tb05457.x.
19. Falcão A, Vaz-da-Silva M, Gama H, Nunes T, Almeida L, Soares-da-Silva P. Effect of eslicarbazepine acetate on the pharmacokinetics of a combined ethinylestradiol/levonorgestrel oral contraceptive in healthy women. Epilepsy Res. 2013;105(3):368–76. https://doi.org/10.1016/J.EPLEPSYRES.2013.02.020.
20. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. Epileptic Disord. 2014;16(4):409–31. https://doi.org/10.1684/epd.2014.0714.
21. Back DJ, Bates M, Bowden A, et al. The interaction of phenobarbital and other anticonvulsants with oral contraceptive steroid therapy. Contraception. 1980;22(5):495–503 http://www.ncbi.nlm.nih.gov/pubmed/7471739. Accessed 5 Apr 2017.
22. Shane-McWhorter L, Cerveny JD, MacFarlane LL, Osborn C. Enhanced metabolism of levonorgestrel during phenobarbital treatment and resultant pregnancy. Pharmacotherapy. 1998;18(6):1360–4 http://www.ncbi.nlm.nih.gov/pubmed/9855340. Accessed 12 Aug 2018.
23. Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. Epilepsia. 1997;38(3):317–23. https://doi.org/10.1111/j.1528-1157.1997.tb01123.x http://www.ncbi.nlm.nih.gov/pubmed/9070594. Accessed 24 June 2018.
24. Eldon MA, Underwood BA, Randinitis EJ, Sedman AJ. Gabapentin does not interact with a contraceptive regimen of norethindrone acetate and ethinyl estradiol. Neurology. 1998;50(4):1146–8. https://doi.org/10.1212/WNL.50.4.1146.
25. Cawello W, Rosenkranz B, Schmid B, Wierich W. Pharmacodynamic and pharmacokinetic evaluation of coadministration of lacosamide and an oral contraceptive (levonorgestrel plus ethinylestradiol) in healthy female volunteers. Epilepsia. 2013;54(3):530–6. https://doi.org/10.1111/epi.12085.
26. Ragueneau-Majlessi I, Levy RH, Janik F. Levetiracetam does not alter the pharmacokinetics of an oral contraceptive in healthy women. Epilepsia. 2002;43(7):697–702. https://doi.org/10.1046/j.1528-1157.2002.57701.x.
27. Sidhu J, Job S, Singh S, Philipson R. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. Br J Clin Pharmacol. 2006;61(2):191–9. https://doi.org/10.1111/j.1365-2125.2005.02539.x.
28. Crawford P, Chadwick D, Cleland P, et al. The lack of effect of sodium valproate on the pharmacokinetics of oral contraceptive steroids. Contraception. 1986;33(1):23–9 http://www.ncbi.nlm.nih.gov/pubmed/3082590. Accessed 5 Apr 2017.
29. Griffith SG, Dai Y. Effect of zonisamide on the pharmacokinetics and pharmacodynamics of a combination ethinyl estradiol-norethindrone oral contraceptive in healthy women. Clin Ther. 2004;26(12):2056–65. https://doi.org/10.1016/j.clinthera.2004.11.019.
30. Gaffield ME, Culwell KR, Lee CR. The use of hormonal contraception among women taking anticonvulsant therapy. Contraception. 2011;83(1):16–29. https://doi.org/10.1016/j.contraception.2010.06.013.
31. Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. U.S. medical eligibility criteria for contraceptive use, 2016. MMWR Recomm Rep. 2016;65(3):1–103. https://doi.org/10.15585/mmwr.rr6503a1.
32. O'Brien MD, Guillebaud J. Contraception for women with epilepsy. Epilepsia. 2006;47(9):1419–22. https://doi.org/10.1111/j.1528-1167.2006.00671.x.
33. Davis AR, Westhoff CL, Stanczyk FZ. Carbamazepine coadministration with an oral contraceptive: effects on steroid pharmacokinetics, ovulation, and bleeding. Epilepsia. 2011;52(2):243–7. https://doi.org/10.1111/j.1528-1167.2010.02917.x.
34. Fattore C, Cipolla G, Gatti G, Limido GL, Sturm Y, Bernasconi C, et al. Induction of ethinylestradiol and levonorgestrel metabolism by oxcarbazepine in healthy women. Epilepsia. 1999;40(6):783–7. https://doi.org/10.1111/j.1528-1157.1999.tb00779.x.
35. McCann MF, Potter LS. Progestin-only oral contraception: a comprehensive review. Contraception. 1994;50(6 Suppl 1):S1–195 http://www.ncbi.nlm.nih.gov/pubmed/10226677. Accessed 29 June 2018.
36. Kinney MO, Morrow J, Patterson CC, Campbell E, Russell A, Smithson HW, et al. Changing antiepilepsy drug-prescribing trends in women with epilepsy in the UK and Ireland and the impact on major congenital malformations. J Neurol Neurosurg Psychiatry. 2018:jnnp-2017-317368. https://doi.org/10.1136/jnnp-2017-317368.
37. Vélez-Ruiz NJ, Pennell PB. Issues for women with epilepsy. Neurol Clin. 2016;34(2):411–25. https://doi.org/10.1016/j.ncl.2015.11.009.
38. Herzog AG, Mandle HB, Cahill KE, Fowler KM, Hauser WA, Davis AR. Contraceptive practices of women with epilepsy: findings of the epilepsy birth control registry. Epilepsia. 2016;57(4):630–7. https://doi.org/10.1111/epi.13320.
39. Johnson EL, Burke AE, Wang A, Pennell PB. Unintended pregnancy, prenatal care, newborn outcomes, and breastfeeding in women with epilepsy. Neurology. 2018;91:e1031–9. https://doi.org/10.1212/WNL.0000000000006173.
40. Espinera AR, Gavvala J, Bellinski I, et al. Counseling by epileptologists affects contraceptive choices of women with epilepsy. Epilepsy Behav. 2016;65:1–6. https://doi.org/10.1016/j.yebeh.2016.08.021.
41. Bounds W, Guillebaud J. Observational series on women using the contraceptive Mirena concurrently with anti-epileptic and other enzyme-inducing drugs. J Fam Plan Reprod Health Care. 2002;28(2):78–80. https://doi.org/10.1783/147118902101195992.
42. Lazorwitz A, Davis A, Swartz M, Guiahi M. The effect of carbamazepine on etonogestrel concentrations in contraceptive implant users. Contraception. 2017;95(6):571–7. https://doi.org/10.1016/J.CONTRACEPTION.2017.03.004.
43. Haukkamaa M. Contraception by NORPLANTR subdermal capsules is not reliable in epileptic patients on anticonvulsant treatment. Contraception. 1986;33(6):559–65. https://doi.org/10.1016/0010-7824(86)90044-2.
44. Pfizer. Pfizer Package leaflet: Information for the patient Depo-Provera 150 mg/ml sterile suspension for injection medroxyprogesterone acetate. 2018. https://www.medicines.org.uk/emc/files/pil.6721.pdf?filename=PIL.6721.pdf. Accessed 5 July 2018.
45. Mattson RH, Cramer JA, Caldwell BV, Siconolfi BC. Treatment of seizures with medroxyprogesterone acetate: preliminary report. Neurology. 1984;34(9):1255–8 http://www.ncbi.nlm.nih.gov/pubmed/6540415. Accessed 8 Nov 2017.
46. Schwartz JL. Release of progestin-only emergency contraception. Curr Womens Health Rep. 2001;1(3):191–5 http://www.ncbi.nlm.nih.gov/pubmed/12112969. Accessed 29 June 2018.
47. O'Brien MD, Gilmour-White SK. Management of epilepsy in women. Postgrad Med J. 2005;81(955):278–85. https://doi.org/10.1136/pgmj.2004.030221.
48. Sabers A, Buchholt JM, Uldall P, Hansen EL. Lamotrigine plasma levels reduced by oral contraceptives. Epilepsy Res. 2001;47(1):151–4. https://doi.org/10.1016/S0920-1211(01)00305-9.
49. Wegner I, Edelbroek PM, Bulk S, Lindhout D. Lamotrigine kinetics within the menstrual cycle, after menopause, and with oral contraceptives. Neurology. 2009;73(17):1388–93. https://doi.org/10.1212/WNL.0b013e3181bd8295.

50. Reimers A, Helde G, Brodtkorb E. Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. Epilepsia. 2005;46(9):1414–7. https://doi.org/10.1111/j.1528-1167.2005.10105.x.
51. Herzog AG, Blum AS, Farina EL, Maestri XE, Newman J, Garcia E, et al. Valproate and lamotrigine level variation with menstrual cycle phase and oral contraceptive use. Neurology. 2009;72(10):911–4. https://doi.org/10.1212/01.wnl.0000344167.78102.f0.
52. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med. 2009;360(16):1597–605. https://doi.org/10.1056/NEJMoa0803531.
53.• Davis AR, Saadatmand HJ, Pack A. Women with epilepsy initiating a progestin IUD: a prospective pilot study of safety and acceptability. Epilepsia. 2016;57(11):1843–8. https://doi.org/10.1111/epi.13559 **Prospective study of progestin IUD use in women with epilepsy.**
54. Lotte J, Grothe S, Kluger G. Seizure freedom in patients with Dravet syndrome with contraceptives: a case report with two patients. Neuropediatrics. 2018;49:276–8. https://doi.org/10.1055/s-0038-1636999.
55. Herzog AG. Differential impact of antiepileptic drugs on the effects of contraceptive methods on seizures: interim findings of the epilepsy birth control registry. Seizure. 2015;28:71–5. https://doi.org/10.1016/j.seizure.2015.02.011.
56. Mandle HB, Cahill KE, Fowler KM, Hauser WA, Davis AR, Herzog AG. Reasons for discontinuation of reversible contraceptive methods by women with epilepsy. Epilepsia. 2017;58(5):907–14. https://doi.org/10.1111/epi.13734.
57. Herzog AG, Mandle HB, Cahill KE, Fowler KM, Hauser WA. Differential impact of contraceptive methods on seizures varies by antiepileptic drug category: findings of the Epilepsy Birth Control Registry. Epilepsy Behav. 2016;60:112–7. https://doi.org/10.1016/j.yebeh.2016.04.020.
58. Harden CL, Herzog AG, Nikolov BG, Koppel BS, Christos PJ, Fowler K, et al. Hormone replacement therapy in women with epilepsy: a randomized, double-blind, placebo-controlled study. Epilepsia. 2006;47(9):1447–51. https://doi.org/10.1111/j.1528-1167.2006.00507.x.