Published in final edited form as:

Expert Rev Neurother. 2017 February ; 17(2): 129–134. doi:10.1080/14737175.2016.1243472.

Do oral contraceptives increase epileptic seizures?

Doodipala Samba Reddy

Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M University Health Science Center, Bryan, TX 77807, USA

Abstract

Introduction—Hormonal contraceptives are used by over 100 million people worldwide. Recently, there has been an emerging interest in studying the potential impact of oral contraceptives (OCs) on certain neurological conditions. It has been suspected for some time that hormonal birth control increases seizure activity in women with epilepsy, but there is little supportive data.

Areas Covered—Literature from PubMed and online sources was analyzed with respect to hormonal contraception and epilepsy or seizures. New evidence indicates that OCs can cause an increase in seizures in women with epilepsy. The epilepsy birth control registry, which surveyed women with epilepsy, found that those using hormonal contraceptives self-reported 4.5 times more seizures than those that did not use such contraceptives. A preclinical study confirmed these outcomes wherein epileptic animals given ethinyl estradiol, the primary component of OCs, had more frequent seizures that are more likely to be resistant.

Expert Commentary—OC pills may increase seizures in women with epilepsy and such refractory seizures are more likely to cause neuronal damage in the brain. Thus, women of child bearing age with epilepsy should consider using non-hormonal forms of birth control to avoid risks from OC pills. Additional research into the mechanisms and prospective clinical investigation are needed.

Keywords

Oral contraceptives; epilepsy; women with epilepsy; seizure; estradiol

1. Introduction

Epilepsy affects an estimated 65 million people worldwide, including an estimated 25 million women. There are approximately 1.2 million women of childbearing age with epilepsy in the USA (1–3). Epilepsy, which is typified by recurrent unprovoked seizures, is associated with special concerns for many of these women. Since hormones are known to

Correspondence address: D. Samba Reddy, Ph.D., R.Ph., FAAPS, FAAAS, Professor, Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M University Health Science Center, 2008 Medical Research and Education Building, 8447 State Highway 47, Bryan, TX 77807-3260, Phone: 979-436-0324, red dy@medicine.tamhsc.edu.

Declaration of Interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

affect seizures, many women report that their seizure patterns change at puberty, at certain phases of the menstrual cycle and with menopause. This is clearly evident in women with certain types of epilepsies, such as catamenial epilepsy and other hormonally-sensitive syndromes. The natural fluctuation in steroid hormones that occurs during the menstrual cycle significantly influences seizure patterns and can potentially influence drug therapy (4–6). Although many women experience worsening of seizures, some improve during menopause and pregnancy.

Antiepileptic drugs (AEDs) are used for symptomatic control of seizures; however, only two-thirds of epilepsy patients can be successfully treated by current AEDs (7–9). People with medication-resistant or refractory epilepsy suffer from consequences of recurrent seizures, which could damage the brain and adversely impact the quality of life. This is evident in women with certain types of epilepsies, such as catamenial epilepsy and other hormonally-sensitive syndromes. Hormonal contraceptive management in women with epilepsy is critical owing to the potential maternal and fetal risks if contraception or seizure management fails. An estimated 10 million women in the USA and 100 million women worldwide use hormonal contraceptives (10). There is strong evidence of interactions between hormonal contraceptives and some marketed AEDs, including lamotrigine (11–16). Moreover, many women are unaware of risks associated with hormonal contraceptives. The word “seizure” has been listed as a potential side effect of many contraceptives. While numerous previous articles state that there is little negative impact on seizures (17–19), there are few acceptable studies in support of such conclusion. Therefore, the impact of contraceptives in epilepsy is being investigated by retrospective studies. This article briefly discusses the emerging reports on the risk of epileptic seizures in women with epilepsy on systemic hormonal contraception.

2. Hormonal Contraceptives and Epilepsy

Contraceptive management in women with epilepsy is critical owing to the potential maternal and fetal risks if contraception or seizure management fails. There are two categories of birth-control options for women: hormonal and non-hormonal methods. Non-hormonal contraceptive (NHC) methods include intrauterine devices, barrier methods, such as condoms, diaphragms and cervical caps, as well as the rhythm method. A wide range of hormonal methods of contraception (HC) are available (19). Long-acting hormonal contraceptives include injectable progestogens, subdermal implants and hormone-releasing devices. The efficacy of agents such as oral contraceptives (OCs), also known as combined OC pills, and contraceptive patches, are highly dependent on correct use and individual lifestyles. The OCs are among the most widely used agents. Designed to simulate the 28 days of the natural menstrual cycle, most OCs consist of an estrogenic and/or a progestogenic agent.

A variety of OCs are available, with substantially different components, doses, and durations (Table 1). Two types of OC pills are widely available: combination pills and progestogen-only pills. The combined daily OC pill is composed of low dose synthetic estrogen and progestogen. They are usually taken for 21 days with a 7-day gap (usually filled with either sugar or iron pills), during which withdrawal bleeding occurs. Currently available combined

OCs can be classified into three types: monophasic (only one dose of estrogen and progestogen during the 21 days), biphasic (varying doses of estrogen and progestogen) and triphasic (varying doses of estrogen and progestogen) (Table 1). In monophasic OCs, fixed amounts of the estrogen and progestogen are present in each pill, which is taken daily for 21 days, followed by a 7-day period with placebo (sugar) pills or iron preparations. The biphasic OC, such as Mircette (Kariva), contains 21 pills of fixed amounts of estrogen (0.02 mg ethinyl estradiol) and progestogen (0.15 mg desogestrel) and 2 placebo pills (rather than the regular 7 placebo pills), and 5 pills of low dose estrogen (0.01 mg ethinyl estradiol). The triphasic OCs, such as Ortho Tri-Cyclen and Ortho-Novum, provide 3 different pills containing varying amounts of estrogen and progestogen (7 days each regimen), to be taken at different times during the 28-day cycle.

The use of AEDs is the mainstay for the management of seizures in women with epilepsy. There are many factors to consider in the selection of contraception since some AEDs may affect the efficacy of OCs owing to pharmacokinetic interaction (20). These interactions between AEDs and OCs can influence drug efficacy and seizure control. Based on hepatic metabolism, AEDs can be classified as enzyme-inducing and enzyme non-inducing types (Table 2). The majority of AEDs are eliminated via hepatic CYP isoenzymes, especially CYP3A4. Some AEDs, such as carbamazepine, felbamate, topiramate, and oxcarbazepine, are mainly metabolized by the CYP3A4 enzyme system, which is also the primary enzyme metabolizing estrogens and progestogens (Figure 1). These AEDs can increase the activity of CYP3A4. Phenytoin is metabolized via CYP 2C9 and 2C19, but it induces CYP3A4. Induction of the CYP3A4 system increases the metabolism of estrogenic and progestogenic components of OCs and drastically reduces their circulating levels (19). This could lead to reduced efficacy of OCs when taken together. Therefore, AEDs that do not induce CYP3A4 are less likely to interact with OCs, and have minimal impact on hormonal contraception.

3. Oral Contraceptives Increases Epileptic Seizures

Although it is known that steroid hormones and neurosteroids can affect seizure susceptibility (5, 21), there is limited information on the potential impact of OCs on seizures in women with epilepsy. A recent study suggests that OCs may exacerbate seizures (Herzog, 2015); however, previous reports mostly attest lack of evidence to support this premise (5, 17, 22). A large cohort study showed that OCs do not increase the incidence of epilepsy (23). This study has some limitations. The study was from the Oxford-Family Planning Association, which included 17,032 women, but only 82 women with diagnosis of epilepsy or convulsion. In fact, the study excluded women known to have suffered from epilepsy or convulsions before entry into the study. Thus, this study is actually very limited as it excluded most women with epilepsy since only those with new onset were included. These conflicting reports, therefore, have raised serious concerns regarding the actual impact of OCs on the risk of seizures in women with epilepsy. Clinical evidence is very limited warranting further studies to confirm or negate the effect of OCs on seizures in women with epilepsy.

Recently, Herzog and colleagues reported the findings of the Epilepsy Birth Control Registry (EBCR), a large, community-based survey of women with epilepsy (24, 25). The

EBCR enrolled women with epilepsy between ages 18 and 47 who had a history of using at least one form of contraception while on AED therapy. About 1,144 women who completed the survey reported a total of 2,712 contraceptive experiences. Individuals were directed to the survey from various referral sources such as epilepsy organization websites, social media, internet searches and study brochures posted in clinics. The survey asked women about the impact of various contraceptive methods on seizures, stratified by AED type and other questions to gather data on type of contraception. Respondents had the option to reply that their contraceptive method seemed to increase, decrease, or not change their seizure number. The EBCR pilot study reports that HC is associated with a broader dynamic range of seizure responses manifested by a significantly greater risk for both seizure increase and decrease than NHC, with the relative risk for an increase in seizures predominating (25). Systematic analysis of results showed that more women with epilepsy reported a change in seizures on hormonal contraceptives (28.2%) than on non-hormonal contraceptives (9.7%), which yielded a relative risk of about 4.5 times for an increased number of seizures while on hormonal contraception, compared with non-hormonal contraception (24). The risk for greater seizure frequency on hormonal contraceptives of all types was 6.75-fold higher, when compared specifically with barrier contraception.

In analyses of specific types of hormonal contraceptives within the EBCR study, women using a hormonal patch reported a 68% greater incidence of seizure increases, compared with women using combined oral contraceptive pills. Patients using a progestin-only pill had a 62% higher rate of seizure increases. In comparison to combined pills, both hormonal patch and progestin-only pills had a greater risk ratio for seizure increase (25–27), suggesting non-oral progesterone contraceptives may have less effect on seizure frequency and also the fact that some women have reduced seizure frequency on such contraception methods.

In a second analysis of the EBCR results, Herzog and colleagues examined the frequencies of seizure incidences on hormonal and non-hormonal contraceptives, stratifying them by the type of AED the women used when starting a particular contraceptive method. Seizure increase was greater for hormonal than non-hormonal contraception for each antiepileptic drug category. On hormonal contraception, relative to the non-enzyme-inducing antiepileptic drug category which had the lowest rate, each of the other categories had significantly greater risks for seizure increase, especially the enzyme inhibiting category. Women on an enzyme-inhibiting drug, valproate, had the highest (29%) rate of increased seizures when starting a hormonal contraceptive (26).

There are some caveats for the interpretation of findings from the EBCR study. Like other surveys, internet-based surveys are subject to biases, and the EBR may be able to attract a preponderance of responses from women who are better educated than the general population. In addition, the survey collects data retrospectively and with some omissions. Nevertheless, the survey results are striking because they represent a powerful data set from a large, community-based source which is large enough to make analysis of critical clinical variables that affect the potential interactions between contraceptive types, antiepileptic drug classes, and the diverse number of epilepsy subtypes (27).

4. Potential Mechanisms of OCs Exacerbation of Seizures

The precise mechanisms by which hormonal contraceptives may increase epileptic seizures remain unknown. Despite the extensive use of hormonal contraception, there is a paucity of evidence regarding the neuroactive properties of the synthetic steroid constituents of OCs. Steroid hormones can affect the structure and function of neuronal networks by targeting complex target systems and pathways (Figure 1). The neuronal excitability mechanisms of estrogens are complex. Physiological receptors for estrogens include multiple membrane-associated and cell nuclear receptors (ER α and ER β). Moreover, the nuclear receptors can also localize to the plasma membrane, where they can activate numerous signaling pathways. Estradiol can also activate a G-protein coupled membrane estrogen receptor with actions on many downstream signal transduction cascades (21). Apart from classical estrogen receptor-mediated effects, estradiol affects neuronal excitability due to its organizational effects on synaptic structure and function (28). Estrogens are known to cause excitatory effects and can increase epileptic seizures (29–31). Intravenous infusion of estradiol was associated with rapid interictal epileptiform activity in women with epilepsy (31). Such excitatory effects may affect seizure risk in women with epilepsy taking OC pills. This premise is consistent with the EBCR study that reported that the highest risk occurred with hormonal patch (25), the only subcategory which is known to produce substantially higher serum levels of ethinyl estradiol than OC pills (32, 33). Thus, it is likely that greater levels of ethinyl estradiol produced by the patch may account for its relatively greater risk for seizure increase than OCs.

Ethinyl estradiol (EE) is a major estrogen constituent in OCs including monophasic, biphasic, triphasic and extended-cycle regimens (19). However, there is little basic data to suggest that EE may have neuroexcitatory properties similar to estradiol (21). Recently, we investigated the pharmacological effect of EE on epileptogenesis and kindled seizure activity in female mice using the hippocampus-kindling model (34). Animals were stimulated daily with or without EE until generalized stage 5 seizures were elicited. In acute studies, EE caused a significant decrease in the afterdischarge threshold and increased the incidence and severity of seizures in fully-kindled animals. In chronic (21 day) studies, EE treatment caused a greater susceptibility to kindled seizures. In addition, EE therapy significantly increased the rate of epileptogenesis to reach stage 5 seizures in naïve (non-epileptic) animals (34). These excitatory effects of EE on the hippocampus kindling are consistent with observations in previous studies with estradiol (35–37). Overall, the moderate proconvulsant activity of EE is consistent with clinical reports of increase in seizures with OCs in women with epilepsy.

In addition to direct excitatory impact of EE, it is likely that levels of AEDs may change due to pharmacokinetic interactions (19). OCs may enhance the metabolism of certain AEDs that may lead to an enhanced risk for seizures in this cohort (38). This is likely because non-hormonal contraceptives, which do not affect AED metabolism as much as OCs, are not associated with such risk of seizures. There is little information on whether IUD-delivered hormonal treatments affect AED metabolism. It should be noted that the vaginal ring, as opposed to hormonal IUDs, does result in systemic hormone absorption as evidenced by increased risk of blood clots and stroke. Nevertheless, there are many underlying

mechanisms whereby EE affects seizure susceptibility. Animals chronically exposed to estradiol have shown increased number and density of dendritic spines and excitatory synapses on hippocampal neurons (39–41). This mechanism increases the synchronization of synaptically driven neuronal firing in the hippocampus and could be relevant to EE's proconvulsant effects in animal models. EE may also increase excitability through modulation of neuropeptides and increased levels of brain-derived neurotrophic factor in the hippocampus (21). In addition to nuclear estrogen receptors, the effects of EE could arise due to interaction with membrane estrogen receptors. The rapid onset of EE may be due to its direct interactions at the membrane level or through a post-membrane secondary messenger cascades that affect neuronal excitability (42, 43).

Progesterone has antiseizure properties and may influence the overall effect of EE (28). However, the outcomes from a recent Phase III clinical trial of progesterone therapy are in contrast to the expectation (44). The study assessed the therapeutic benefit of progesterone therapy in the second half of the menstrual cycle in women with intractable epilepsy, including catamenial or non-catamenial categories. However, progesterone treatment offered little significant efficacy in reduction of seizure frequency. Post hoc analysis revealed that women who experienced perimenstrual catamenial exacerbation were indeed significantly responsive to progesterone therapy. Analysis of plasma levels of the progesterone-derived neurosteroid allopregnanolone support this neurosteroid as a mediator of seizure reduction in progesterone-treated women who have a substantial level of perimenstrually exacerbated seizures (45).

5. Expert commentary

There are a variety of serious side effects that may be associated with the birth control pills including seizures. In fact, there are many lawsuits against the manufacturers involving birth control pills. Neurologists suspected for some time that hormonal birth control increases seizure activity in women with epilepsy, but now we know what part of the contraceptive is problematic. It is becoming clear that certain types of hormonal contraceptives can cause an increase in seizures in women with epilepsy—that is the suggestion from a recent study published report (25). In this study, which surveyed women with epilepsy as part of the EBCR, Herzog and his colleagues have found that those using hormonal contraceptives self-reported 4.5 times more seizures than those that did not use oral contraceptives. Hence, it is likely that seizures could increase when women start a hormonal contraceptive. Consistent with this premise, a recent study looked at the pharmacological effect of ethinyl estradiol, the primary component of oral contraceptives, on the epileptic brain (34). The study found that when epileptic mice received ethinyl estradiol they not only had more frequent seizures, but the seizures were more likely to be resistant. It is more difficult to control seizures in women once they reach sexual maturity.

The hormones that control menstruation and pregnancy can trigger seizures. Consequently, women often experience more seizures in the week before their period due to the change in these hormones. This type of neuroendocrine condition is referred as catamenial epilepsy. While epilepsy affects men more than women, women with epilepsy tend to experience seizures more frequently than men and women's seizures are more likely to be resistant to

some antiepileptic drugs. Such refractory seizures are more likely to permanently damage the brain. Some parts of the brain are more vulnerable to damage than others, for example the hippocampus, which has a role in regulating memory and spatial orientation. Therefore, refractory seizures are frequently associated with cognitive impairments that can affect person's normal functioning. It should be noted that not all OCs have the same effects, and some non-oral contraceptives, such as depot medroxyprogesterone or dermic implants, may be a better alternative than OCs. As a result of the study, Herzog and colleagues recommend that women of child bearing age with epilepsy speak with their neurologist or endocrinologist about using non-hormonal forms of birth control such as a copper intrauterine device or barrier methods like condoms.

6. Five-year view

Since uncontrolled or pharmacoresistant seizures, such as those occurring in women with epilepsy, tend to permanently damage the neurons in the brain, new or adjunct therapeutic strategies will be explored within the next few years. More findings and data will become available within next 5 years from the EBCR study. Based on findings from the EBCR-enrolled women with epilepsy, clinical investigators may conduct prospective studies and confirm some key outcomes within the next five years. The new adjunct treatments include drugs that can prevent or reduce the hormonally-sensitive seizures and combination therapies that effectively control intractable seizures and pharmacoresistance seizures. Isobolographic and related pharmacological studies may aid in identifying new antiepileptic drug combinations that can exert symptomatic control of seizures in women with epilepsy. New developments such as non-hormonal contraception may become available for women with epilepsy who need to take enzyme-inducing AEDs.

Acknowledgments

Funding

The author is funded by the NIH grants NS051398 and NS083460.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1. El-Sayed YY. Obstetric and gynecologic care of women with epilepsy. *Epilepsia*. 1998; 39(8):S17–S2.
2. Morrell MJ. Reproductive and metabolic disorders in women with epilepsy. *Epilepsia*. 2003; 44(4): 11–20.
3. Harden CL, Pennell PB, Koppel BS, et al. Management issues for women with epilepsy – focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009; 50:1247–1255. [PubMed: 19507305]

- 4 ••. Reddy DS. The role of neurosteroids in the pathophysiology and treatment of catamenial epilepsy. *Epilepsy Res.* 2009; 85:1–30. Comprehensive review on the role of endogenous neurosteroids in experimental animals and clinical catamenial seizures in women with epilepsy. [PubMed: 19406620]
5. Reddy DS. Neurosteroids and their role in sex-specific epilepsies. *Neurobiol Dis.* 2014a; 2:198–209.
- 6 •. Reddy DS. Catamenial Epilepsy: Discovery of an extrasynaptic molecular mechanism for targeted therapy. *Front Cell Neurosci.* 2016; 10(101):1–12. Expert and authoritative review of novel therapeutic strategy for catamenial epilepsy. [PubMed: 26858601]
7. Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs. *Nat Rev Neurosci.* 2004; 5:553–564. [PubMed: 15208697]
- 8 •. French JA, Pedly TA. Initial management of epilepsy. *N Engl J Med.* 2008; 359:166–176. Expert and authoritative review of various strategies and current pharmacotherapy of epilepsy. [PubMed: 18614784]
9. Reddy DS. Clinical pharmacology of current antiepileptic drugs. *Int J Pharm Sci Nanotech.* 2014b; 7(1):2305–2319.
10. Hatcher, RA., Nelson, A. Combined hormonal contraceptive methods. In: Hatcher, RA., editor. *Contraceptive Technology*. 18th. Ardent Media; NY, USA: 2004. p. 391-460.
- 11 •. Crawford P. Best practice guidelines for the management of women with epilepsy. *Epilepsia.* 2005; 46(9):117–124. Insightful review on managing epilepsy in women of childbearing age. [PubMed: 16302885]
- 12 •. Sabers A, Öhman I, Christensen J, Tomson T. Oral contraceptives reduce lamotrigine plasma levels. *Neurol.* 2003; 61:570–571. First study to demonstrate that lamotrigine levels were reduced by 50% in women taking this drug in combination OCs.
13. Herzog AG, Blum AS, Farina EL, Maestri XE, Newman J, Garcia E, Krishnamurthy KB, Hoch DB, Replansky S, Fowler KM, Smithson SD, Dworetzky BA, Bromfield EB. Valproate and lamotrigine level variation with menstrual cycle phase and oral contraceptive use. *Neurol.* 2009; 72:911–914.
14. Wegner I, Wilhelm AJ, Lambrechts DA, Sander JW, Lindhout D. Effect of oral contraceptives on lamotrigine levels depends on comedication. *Acta Neurol Scand.* 2014; 129(6):393–8. [PubMed: 24571554]
15. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disord.* 2014; 16(4):409–32. [PubMed: 25515681]
16. Stockis A, Watanabe S, Fauchoux N. Interaction between brivaracetam (100mg/day) and a combination oral contraceptive: a randomized, double-blind, placebo-controlled study. *Epilepsia.* 2014; 55(3):27–31.
17. Crawford P, Chadwick D, Cleland P. The lack of effect of sodium valproate on the pharmacokinetics of oral contraceptive steroids. *Contraception.* 1986; 33:23–29. [PubMed: 3082590]
- 18 ••. Harden CL, Leppik I. Optimizing therapy of seizures in women who use oral contraceptives. *Neurol.* 2006; 67(4):S56–S58. Insightful review on the potential interactions between oral contraceptives (OCs) and antiepileptic drugs with expert clinical input for treatment optimization.
- 19 •. Reddy DS. Clinical pharmacokinetic interactions between antiepileptic drugs and hormonal contraceptives *Expert Rev. Clin Pharmacol.* 2010; 3(2):183–192. Excellent review on pharmacokinetic discussion on OCs and AEDs.
20. Crawford P, Chadwick DJ, Martin C. The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids. *Br J Clin Pharmacol.* 1990; 30:892–896. [PubMed: 2126946]
21. Scharfman HE, MacLusky NJ. The influence of gonadal hormones on neuronal excitability, seizures and epilepsy in the female. *Epilepsia.* 2006; 47:1423–1440. [PubMed: 16981857]
22. Harden CL, Leppik I. Optimizing therapy of seizures in women who use oral contraceptives. *Neurol.* 2006; 67(4):S56–S58.
23. Vessey M, Painter R, Yeates D. Oral contraception and epilepsy. *Contraception.* 2002; 66:77–79. [PubMed: 12204778]

- 24 ••. 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; 28:71–75. Expert and authoritative review of interim data from the Epilepsy Birth Control Registry study. [PubMed: 25770029]
25. 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*. 2016a; 57:630–637. [PubMed: 26880331]
- 26 ••. 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*. 2016b; 60:112–117. First original report stating that hormonal contraceptives may increase epileptic seizures from a large community-based study. [PubMed: 27206228]
27. Zoler ML. Hormonal contraceptives may increase epileptic seizures. *Neurol Rev*. 2016;30–33.
28. Reddy DS. Role of hormones and neurosteroids in epileptogenesis. *Front Cell Neurosci*. 2013; 31(115):1–13.
29. Bäckström T. Epileptic seizures in women related to plasma estrogen and progesterone during the menstrual cycle. *Acta Neurol Scand*. 1976; 54:321–347. [PubMed: 973554]
30. Jacono JJ, Robinson J. The effects of estrogen, progesterone, and ionized calcium on seizures during the menstrual cycle in epileptic women. *Epilepsia*. 1987; 28:571–577. [PubMed: 3653063]
31. Logothetis J, Harner R, Morrel F. The role of estrogens in catamenial exacerbation of epilepsy. *Neurol*. 1959; 9:352–360.
32. Sibai BM, Odland V, Meador ML, Shangold GA, Fisher AC, Creasy GW. A comparative and pooled analysis of the safety and tolerability of the contraceptive patch (Ortho Evra/Evra). *Fertil Steril*. 2002; 77(2.2):S19–26.
33. Dore DD, Norman H, Loughlin J, Seeger J. Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users. *Contraception*. 2010; 81:408–13. [PubMed: 20399947]
- 34 ••. Younus I, Reddy DS. Seizure facilitating activity of the oral contraceptive ethinyl estradiol. *Epilepsy Res*. 2016; 121:29–32. This data shows for the first time that EE exacerbates seizures in epileptic animals. [PubMed: 26874323]
35. Buterbaugh GG. Estradiol replacement facilitates the acquisition of seizures kindled from the anterior neocortex in female rats. *Epilepsy Res*. 1989; 4:207–215. [PubMed: 2612493]
36. Edwards HE, Burnham WM, MacLusky NJ. Testosterone and its metabolites affect afterdischarge thresholds and the development of amygdala kindled seizures. *Brain Res*. 1999; 838:151–157. [PubMed: 10446327]
37. Reddy DS. Testosterone modulation of seizure susceptibility is mediated by neurosteroids 17 β -estradiol and 3 α -androstenediol. *Neurosci*. 2004; 129:195–207.
38. Herzog AG, Blum AS, Farina EL. Valproate and lamotrigine level variation with menstrual cycle phase and oral contraceptive use. *Neurol*. 2009; 72:911–914.
39. Murphy DD, Cole NB, Greenberger V. Estradiol increases dendritic spine density by reducing GABA neurotransmission in hippocampal neurons. *J Neurosci*. 1998; 18:2550–2559. [PubMed: 9502814]
40. Woolley CS, Weiland NG, McEwen BS. Estradiol increases the sensitivity of hippocampal CA1 pyramidal cells to NMDA receptor-mediated synaptic input: correlation with dendritic spine density. *J Neurosci*. 1997; 17:1848–1859. [PubMed: 9030643]
41. Ruddick CN, Woolley CS. Estrogen regulates functional inhibition of hippocampal CA1 pyramidal cells in the adult female rat. *J Neurosci*. 2001; 21:6532–6543. [PubMed: 11517242]
42. Zadrán S, Qin Q, Bi X, Zadrán H, Kim Y, Foy MR, Thompson R, Baudry M. 17 β -estradiol increases neuronal excitability through MAP kinase-induced calpain activation. *Proc Natl Acad Sci USA*. 2009; 106:21936–21941. [PubMed: 19995977]
43. Roepke TA, Ronnekleiv OK, Kelly MJ. Physiological consequences of membrane-initiated estrogen signaling in the brain. *Front Biosci (Landmark Ed)*. 2001; 16:1560–1573.
44. Herzog AG, Fowler KM, Smithson SD, Kalayjian LA, Heck CN, Sperling MR, Liporace JD, Harden CL, Dworetzky BA, Pennell PB, Massaro JM, Progesterone Trial Study Group.

- Progesterone vs placebo therapy for women with epilepsy: A randomized clinical trial. *Neurol.* 2012; 78:1959–1966.
45. Herzog AG, Frye CA, Progesterone Trial Study Group. Allopregnanolone levels and seizure frequency in progesterone-treated women with epilepsy. *Neurol.* 2014; 83:345–458.

Key Issues

- Contraceptive management in women with epilepsy is a complex and critical issue.
- Although OCs are widely used by many women with epilepsy, little is known about their impact on epileptic seizures.
- New study shows OCs can increase seizures in women with epilepsy. This could impact several thousands of women with epilepsy worldwide.
- Estrogens have neuroexcitatory effects that can exacerbate seizure activity, as shown in preclinical study in epileptic animals.
- While precise mechanisms are unclear, direct and indirect effects of OCs on neuronal targets may be involved in modulating the seizure susceptibility.
- Given the emerging evidence on possible seizure risk with OCs, women of child-bearing age with epilepsy should seek consultation on potential use of non-hormonal forms of contraception.

Figure 1. Potential mechanisms underlying the seizure facilitating effects of hormonal contraceptives

Hormonal contraceptive products, such as oral contraceptives (OCs), affect seizure susceptibility by at least three major mechanisms: (i) Direct non-genomic effects on neuronal targets such as receptors or pathways involved in neuronal excitability and seizure susceptibility (GABA, glutamate and other receptors); (ii) Direct genomic effects on intracellular targets such as steroid receptors or pathways involved in neural genes involved in neuronal structure and function; and (iii) Indirect effects by alteration of metabolism of antiepileptic drugs (AEDs) via induction of hepatic cytochrome P-450 enzyme system, which can lead to pharmacokinetic interactions and thereby reduced therapeutic efficacy when taken together.

Table 1

List of combination oral contraceptive products*.

Monophasic Oral Contraceptives	
Alesse (Lessina, Luter, Aviane)	Levonorgestrel (0.1) + Ethinyl estradiol (0.02)
Lo-Ovral (Cryselle, Low-Ogestrel, Velivet)	Norgestrel (0.3) + Ethinyl estradiol (0.03)
Demulen (Zovia, Kelnor)	Ethinodiol diacetate (1) + Ethinyl estradiol (0.035)
Desogen/ Ortho-Cept (Solia, Apri, Reclipsen)	Desogestrel (0.15) + Ethinyl estradiol (0.03)
Loestrin/ Loestrin-Fe (Microgestin, Junel)	Norethindrone acetate (1) + Ethinyl estradiol (0.02)
Nordette/ Levien (Portia, Levora)	Levonorgestrel (0.15) + Ethinyl estradiol (0.03)
Ortho-Novum/ Medicon (Nortel, Neocon)	Norethindrone (1) + Ethinyl estradiol (0.035)
Ortho-Cyclen (MonoNessa, Previfem, Sprintec)	Norgestimate (0.25) + Ethinyl estradiol (0.035)
Ovcan-35 (Balziva, Femcon, Zenchent)	Norethindrone (0.4) + Ethinyl estradiol (0.035)
Ovral (Ogestrel)	Norgestrel (0.5) + Ethinyl estradiol (0.05)
Yasmin (Ocella)	Drospirenone (3) + Ethinyl estradiol (0.03)
Yaz	Drospirenone (3) + Ethinyl estradiol (0.02)
Biphasic Oral Contraceptives	
Mircette (Kariva)	Desogestrel (0.15) + Ethinyl estradiol (0.02/0.01)
Triphasic Oral Contraceptives	
Ortho Tri-Cyclen (Trisprintec, Tri-Previfem, Tri-Nessa)	Norgestimate (0.18/0.215/0.25) + Ethinyl estradiol (0.035/0.035/0.035)
Ortho-Novum-7/7/7	Norethindrone (0.5/0.75/1) + Ethinyl estradiol (0.035/0.035/0.035)
Tri-Levlen/ Triphasil (Enpresse, Trivora)	Levonorgestrel (0.05/.075/0.125) + Ethinyl estradiol (0.03/0.04/0.03)
Tri-Norinyl (Arlinelle)	Norethindrone (0.5/1/0.5) + Ethinyl estradiol (0.035/0.035/0.035)
Extended cycle regimens	
Seasonale (Quasense, Jolessa)	Levonorgestrol (0.15) + Ethinyl estradiol (0.05/0.01)
Seasonique	Levonorgestrol (0.15) + Ethinyl estradiol (0.03/0.01)

* Numbers within the parenthesis represent composition in mg.

Table 2

List of enzyme-inducing and enzyme non-inducing antiepileptic drugs.

<i>Enzyme-inducing antiepileptic drugs (interacts with OCs)</i>	
Carbamazepine (Tegretol)	
Felbamate (Felbatol)	
Lamotrigine (Lamictal)	
Oxcarbazepin (Trileptal)	
Phenobarbitone (Luminal)	
Phenytoin (Dilantin)	
Primidone (Mysoline)	
Topiramate (Topamax)	
<i>Enzyme non-inducing antiepileptic drugs (does not interact with OCs)</i>	
Clonazepam (Rivotril)	
Ethosuximide (Zarontin)	
Gabapentin (Neurontin)	
Levetiracetam (Keppra)	
Pregabalin (Lyrica)	
Tiagabine (Gabitril)	
Valproate (Depakote)	
Vigabatrin (Sabril)	
Zonisamide (Zonegran)	