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Differential impact of contraceptive methods on seizures varies by antiepileptic drug category: Findings of the Epilepsy Birth Control Registry

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ABSTRACT

Purpose: The aim of this study was to determine whether categories of contraception differ in their impact on seizures in women with epilepsy and whether the impact varies by antiepileptic drug category.
Methods: Retrospective survey data came from 2712 contraceptive experiences reported by 1144 women with epilepsy. We compared risk ratios for reports of increase and decrease in seizure frequency on hormonal versus nonhormonal contraception, stratified by antiepileptic drug categories.
Results: More women with epilepsy reported a change in seizures on hormonal (28.2%) than on nonhormonal contraception (9.7%) ($p < 0.0001$). The risk ratio for seizure increase on hormonal (18.7%) versus nonhormonal contraception (4.2%) was 4.47 ($p < 0.0001$). The risk ratio for seizure decrease on hormonal (9.5%) versus nonhormonal contraception (5.5%) was 1.71, $p < 0.0001$. On hormonal contraception, the risk ratio for seizure increase was greater than for decrease (1.98, $p < 0.0001$). In comparison to combined pills, both hormonal patch and progestin-only pills had greater risk ratios for seizure increase. Depomedroxyprogesterone was the only hormonal method with a greater risk ratio for seizure decrease than combined pills. Seizure increase was greater for hormonal than nonhormonal contraception for each antiepileptic drug category ($p < 0.001$). 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 (valproate) category (risk ratio = 2.53, $p = 0.0002$).
Conclusion: The findings provide community-based, epidemiological survey evidence that contraceptive methods may differ in their impact on seizures and that this impact may vary by antiepileptic drug category.

1. Introduction

The Epilepsy Birth Control Registry (EBCR) is a large-scale, web-based survey investigation of the contraceptive practices of women with epilepsy in the community [1]. Initial exploratory findings suggest that approximately one-half of women with epilepsy (WWE) at risk of unplanned pregnancy use hormonal contraception (HC) [1]. The widespread use of HC by this population raises questions regarding seizure safety since some reproductive steroids have neuroactive properties that can affect neuronal excitability and seizure thresholds [2–12]. Moreover, reciprocal pharmacological interactions occur between some reproductive steroids and some antiepileptic drugs (AEDs) that may compromise both contraceptive efficacy and seizure control [13–19]. Nevertheless, large-scale, community-based clinical studies comparing the seizure safety of hormonal contraception to other categories of contraception with typical use in WWE are lacking as are comprehensive evidence-based guidelines for the selection of optimal, safe, and effective contraceptive methods for this special population. The purpose of this part of the EBCR project was to determine whether there is a differential impact of various categories of contraception on seizure frequency in WWE in the community and, if so, whether the impact varies when stratified by AED category.

2. Methods

2.1. Subjects

The subjects were the first 1144 WWE who completed the EBCR web-based survey. 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. Participation in the study required that women be of reproductive age, be between 18

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and 47 years, and report a diagnosis of epilepsy. Women under the age of 18 were excluded because of the difficulty in ascertaining the consent of minors and their guardians online. Detailed demographic, epilepsy, and AED characteristics of the EBCR population have been published in a report of their contraceptive practices [1].

This study was approved by the Western Institutional Review Board as well as the Columbia University Medical Center Institutional Review Board. Online consent was obtained from all participants. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.2. Data collection and definitions

These retrospective data came from 2712 contraceptive experiences reported by the first 1144 WWE who completed the online EBCR survey. Contraceptive methods were broadly classified as systemic hormonal (HC) (which included oral-combined or progestin-only contraceptive pills, patches, vaginal ring, depomedroxyprogesterone, and implanted progestins) versus nonhormonal (NHC) (which included withdrawal, male and female condoms, copper and progestin intrauterine devices, and tubal ligation). This broad classification was parceled further into more specific categories (withdrawal, barrier, hormonal [subcategories: oral, non-oral, combined, progestin-only], intrauterine device [subcategories: copper, progestin], and tubal ligation). Categories were identified as single-method (e.g., hormonal) or combination (e.g., hormonal and withdrawal). Combinations were designated as hormonal if they included the use of systemic hormones.

We categorized AED treatment as none, monotherapy, or polytherapy. We grouped AEDs into 6 categories based on their effects on enzymatic metabolism: 1) no AED; 2) enzyme-inducing AEDs which included phenobarbital, phenytoin, carbamazepine, oxcarbazepine, and topiramate (>200 mg daily); 3) glucuronidated AEDs which included only lamotrigine; 4) non-enzyme-inducing AEDs which included levetiracetam, zonisamide, gabapentin, topiramate (in dosages ≤200 mg daily), and lacosamide, clobazam, pregabalin, and tiagabine; 5) enzyme-inhibiting AEDs which included only valproate; and 6) mixed categories. Note that valproate was listed in the enzyme-inhibiting AED category although it is also partially glucuronidated. When there was a combination of an AED that affected enzymes and a non-enzyme-inducing AED, the combination was listed by the category that affected enzymes. If the combination was comprised of two or more categories that affect enzymes differently, they were listed as mixed category.

Seizure outcome data were the frequencies of "increase", "decrease", and "no change" responses to the question "Do you think that this method of birth control changed how often you had seizures?" Definitions have been published in greater detail previously [1]. Since there was a congruence of over 99% between the directional changes in seizure frequency and seizure severity, we present only the results for seizure frequency.

2.3. Outcomes

The study was designed to address 4 specific questions regarding the safety of the contraceptive practices of WWE as they relate to seizures:

1. Do the frequencies of reports of changes in seizure frequency differ by the broad categories of HC versus NHC?
2. Are there differences in the frequencies of reports of changes in seizure frequency among the various more specific categories of contraception (withdrawal, barrier, hormonal, intrauterine device, and tubal ligation) and subcategories of hormonal contraception and intrauterine devices?
3. Are frequencies of reports of changes in seizure frequency on HC and NHC affected by the category of AED in use?
4. What are the odds of seizure increase or decrease on various combinations of contraceptive and AED categories?

2.4. Statistical analysis

We determined whether there were differences in the proportions of WWE who reported seizure change on the broad class of HC versus NHC using X^2 analysis (SPSS v23). We compared the risk ratios (RRs) of reports of seizure increase and decrease on HC versus NHC, as well as on the 5 more specific contraceptive categories, using the category with the least impact on seizure frequency as referent. Risk ratios are reported with their 95% CI in parentheses. We carried out separate comparisons for single-method and combination-method categories.

We determined whether there were differences in the proportions of WWE who reported seizure change on the broad class of HC versus NHC, stratified by the first 5 (i.e., nonmixed) AED categories, using X^2 analysis. We compared mixed categories and various AED combinations separately. We determined and compared the RRs for seizure increase and decrease by AED category, separately for HC and NHC, using no AED and also the AED category with the lowest rate of seizure increase and decrease as referent.

We carried out predictor analyses using binary logistic regression separately for seizure increase and decrease, using the categories of contraception and the categories of AEDs, as well as their interactions, as predictor variables. We compared predictor probabilities using odds ratios (ORs).

3. Results

3.1. Differential effects of hormonal versus nonhormonal contraception on seizures

Although the majority of WWE reported no change in seizure frequency with the use of HC (934/1300, 71.8%) and NHC (1275/1412, 90.3%), more WWE reported a change in seizures on HC than NHC (366/1300, 28.2% versus 137/1412, 9.7%; $X^2 = 152.53$, df = 1, $p < 0.0001$). The RR for seizure increase on HC (243/1300, 18.7%) versus NHC (59/1412, 4.2%) was 4.47 (3.40–5.89) ($p < 0.0001$). The RR for seizure decrease on HC (123/1300, 9.5%) versus NHC (78/1412, 5.5%) was 1.71 (1.30-2.25), $p < 0.0001$. Although the RRs for both seizure increase and decrease are greater with HC than NHC, the RR for seizure increase on HC was greater than for decrease (RR = 1.98 (1.61–2.42), $p < 0.0001$), whereas on NHC, there was no significant difference (RR = 0.76 (0.54–1.05), p = NS).

3.2. Differential effects of the various categories and subcategories of contraception on seizures

Table 1 lists the frequencies of seizure increase and decrease by the various single-method categories of contraception. The lowest rate of seizure increase was reported with barrier methods (3.0%), whereas the highest occurred with systemic hormonal methods (19.9%). Fig. 1

Table 1
Frequencies of seizure increase and decrease on various single-method categories of contraception.

	Number of contraceptive experiences (2424)	Number of reports of seizure increase (%)	Number of reports of seizure decrease (%)
Withdrawal	352	18 (5.1%)	12 (3.4%)
Barrier	711	21 (3.0%)	27 (3.8%)
Hormonal	1094	218 (19.9%)	111 (10.1%)
IUD	228	14 (6.1%)	30 (13.2%)
Tubal ligation	39	2 (5.1%)	6 (15.4%)

Data are the frequencies of responses to the question "Do you think that this method of birth control changed how often you had seizures?" Combinations of contraceptive methods (N = 288) are presented separately.

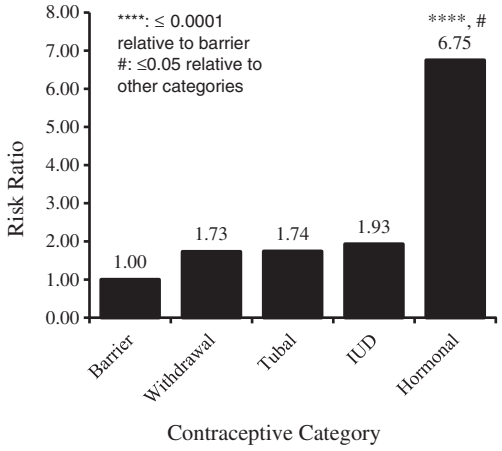

Fig. 1. The risk ratio (RR) for reports of seizure increase was substantially and significantly greater with hormonal contraception than with each of the categories of nonhormonal contraception. In comparison to barrier, which had the lowest rate at 3.0%, hormonal contraception had a RR of 6.75 (95% CI: 4.35–10.45) ($p < 0.0001$).

depicts the RRs for seizure increase with each category of contraception relative to barrier, the one with the lowest rate. The RR for seizure increase was significantly ($p < 0.05$) and substantially greater with HC than with each of the categories of NHC. The greatest RR was for HC relative to barrier (6.75 [4.35–10.45], $p < 0.0001$).

Table 2 lists the frequencies of seizure increase and decrease by the various subcategories of HC. In comparison to the combined pill, which was the most frequently used method and had the lowest rate of reports of seizure increase in the broad HC category, both hormonal patch (RR = 1.68 [1.11–2.56], p = 0.01) and progestin-only pill (RR = 1.62 [1.05–2.49], p = 0.03) had greater RRs for seizure increase. Depomedroxyprogesterone (35/200, 17.5%) was the only HC method with a greater RR for seizure decrease than combined pill (57/635, 9.0%) (RR = 1.95 (1.32–2.88), p = 0.0008).

In a comparison of combinations of contraceptive methods, combinations that included HC (25/206, 12.1%) showed a greater RR for seizure increase than those consisting only of NHC (4/82, 4.9%). The RR was 2.49 (0.89-6.93) (p = 0.0811).

With regard to seizure decrease (Table 1), relative to withdrawal which had the lowest rate of seizure decrease (12/352, 3.4%), the RRs for seizure decrease were greater with tubal ligation (RR = 4.51 [1.79–11.35], p = 0.001), intrauterine device (RR = 3.86 [2.02–7.38], $p < 0.0001$), and HC (RR = 2.98 [1.66–5.33], p = 0.0002) but not barrier (RR = 1.11 [0.57–2.17], p = NS).

In a comparison of combinations of contraception methods for seizure decrease, frequencies of decrease were small and did not show a significant difference (HC combinations (12/206, 5.8%) versus NHC (3/82, 3.7%); RR = 1.59 [0.46–5.50], p = NS).

There were no significant differences in RRs between progestin and copper intrauterine devices for seizure increase (progestin (10/150, 6.7%) versus copper (4/78, 5.1%); RR = 1.30 [0.42–4.01], p = NS) or decrease (progestin (22/150, 14.7%) versus copper (8/78, 10.3%); RR = 1.43 [0.6677–3.0625], p = NS).

3.3. Differential effects of hormonal versus nonhormonal contraception on seizures, stratified by antiepileptic drug category

The frequencies of reports of seizure increase were greater for HC than NHC for each AED category at the $p < 0.001$ level: no AED [28/148 (18.9%) versus 1/85 (1.2%)], enzyme-inducing AED [53/311 (17%) versus 9/385 (2.3%)], glucuronidated AED [53/291 (18.2%) versus 12/344 (3.5%)], non-enzyme-inducing AED [27/232 (11.6%) versus 6/224 (2.7%)], and enzyme-inhibiting AED [25/85 (29.4%) versus 2/79 (2.5%)] (Fig. 2). The mixed category also showed a greater frequency of seizure increase on HC [39/137 (28.5%)] than on NHC [13/191 (6.8%)] ($p < 0.0001$).

The frequencies of reports of seizure increase differed by AED category for HC (p = 0.032) but not for NHC (p = NS) (Table 3). The frequencies of seizure decrease did not differ significantly by AED category for HC or NHC (Table 3). Relative to the frequency of seizure increase reported by WWE for no AED on HC (18.9%), the RR for seizure increase on enzyme-inhibiting AED (29.4%) trended greater (RR = 1.55 (0.97–2.48), p = 0.065), whereas the RR for non-enzyme-inducing AED (11.6%) was less (RR = 0.62 (0.38–1.00), p = 0.05). Relative to non-enzyme-inducing AED (the category that had the lowest frequency of seizure increase on HC (11.6%)), all of the other AED categories showed greater RRs for seizure increase: enzyme-inhibiting AED (RR = 2.53 (1.56–4.10), p = 0.0002), glucuronidated AED (RR = 1.57 (1.02–2.41), p = 0.04), and enzyme-inducing AED (RR = 1.46 (0.95-2.25), p = 0.08). Although seizure decrease did not differ significantly for AED categories relative to no AED on HC, non-enzyme-inducing AED (the category which had the highest frequency of seizure decrease on HC (11.6%)) had a RR that was almost twofold greater than for glucuronidated AED, which had the lowest frequency (6.2%) (RR = 1.89 (1.06–3.33), p = 0.03).

Each AED category showed a greater frequency of reports of seizure increase than decrease on HC except the non-enzyme-inducing AED category: no AED (RR = 2.00 (1.10–3.64), p = .02), enzyme-inducing AED (RR = 1.56 (1.04–2.33), p = 0.03), glucuronidated AED (RR = 2.80 (1.69–4.66), p = 0.0001), non-enzyme-inducing AED (RR = 1.00 (0.61–1.65), p = NS), and enzyme-inhibiting AED (RR = 4.17 (1.80–9.64), p = 0.0009) (Table 3). There was no significant difference between reports of seizure increase and decrease for any AED category on NHC.

Among AED monotherapies, valproate had the most notable differential effect on HC versus NHC. In 69 experiences on valproate with HC, there were 22 (31.9%) reports of seizure increase as compared to no reports (0.0%) of seizure increase in 60 experiences on valproate with NHC (Fisher's exact test: $p < 0.0001$). In contrast, seizure decrease was very similar on HC and NHC: 3/69 (4.3%) on valproate with HC versus 2/60 (3.3%) on valproate with NHC (Fisher's exact test: p = NS). Next came lamotrigine: in 183 experiences on lamotrigine monotherapy with HC, there were 42 (23.0%) reports of seizure increase as compared to 8/223 (3.6%) on lamotrigine with NHC (Fisher's exact test:

Table 2
Comparisons of subcategories and types of hormonal contraception effects on seizures.

			N	Seizure increase (%)	Seizure decrease (%)
Combined	Oral	Combined OCP	635	115 (18.1%)	57 (9.0%)
	Non-oral	Vaginal ring	104	21 (20.2%)	7 (6.7%)
		Hormonal patch	59	18 (30.5%)	5 (8.5%)
Progestin-only	Oral	Progestin OCP	58	17 (29.3%)	5 (8.6%)
	Non-oral	Progestin implant	37	9 (24.3%)	2 (5.4%)
		DMPA	200	38 (19.0%)	35 (17.5%)

In comparison to combined oral contraceptive pill (OCP), the most commonly used hormonal contraceptive method, there was a greater risk ratio (RR) for seizure increase with hormonal patch (RR = 1.68 [95% CI = 1.11–2.56], p = .01) and progestin-only oral contraceptive pill (RR = 1.62 [95% CI = 1.05–2.49], p = .03) and greater RR for seizure decrease with depomedroxyprogesterone (DMPA) (RR = 1.95 [95% CI = 1.32–2.88], p = 0.0008).

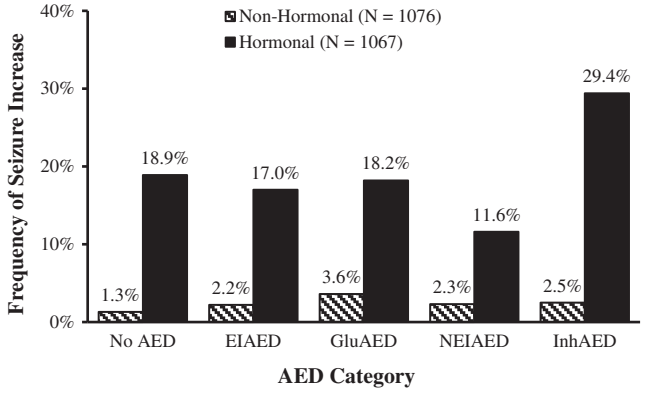

Fig. 2. The frequency of reports of seizure increase was significantly greater ($p < 0.001$) for hormonal contraception than nonhormonal contraception for each AED category (EIAED — enzyme-inducing AED, GluAED — glucuronidated AED [lamotrigine], NEIAED — non-EIAED, InhAED — enzyme-inhibiting AED [valproate], and no AED). Mixed categories are not included. AED categories differed in the frequencies of reports of seizure increase on hormonal contraception ($p = 0.032$) but not on nonhormonal contraception (p = NS). Abbreviations: EIAED = enzyme-inducing AED, GluAED = glucuronidated AED [lamotrigine], NEIAED = non-EIAED, InhAED = enzyme-inhibiting AED [valproate]. Mixed categories are analyzed separately.

$p = 0.0001$). Again, in contrast, seizure decrease did not differ significantly for lamotrigine on HC versus NHC: 7/183 (3.8%) on lamotrigine with HC versus 8/223 (3.6%) on lamotrigine with NHC (Fisher's exact test: p = NS). In a comparison of the two most common AEDs in the non-enzyme-inducing AED category, although levetiracetam had the more favorable profile, there were no significant differences between levetiracetam and zonisamide for seizure increase (levetiracetam (14/124, 11.3%) versus zonisamide (7/42, 16.7%)) or decrease (levetiracetam (11/124, 8.9%) versus zonisamide (2/42, 4.8%)).

Among the AED combinations on HC, only glucuronidated AED + enzyme-inhibiting AED showed a significantly greater RR for seizure increase than no AED (42.3% versus 18.9%) (RR = 2.24 (1.28–3.91), $p = 0.005$).

Table 3
Frequencies of reports of changes in seizure frequency on hormonal contraception, stratified by AED category.

	N on HC	Seizure increase on HC (%)	Seizure decrease on HC (%)	N on NHC	Seizure increase on NHC (%)	Seizure decrease on NHC (%)
No AED	148	28 (18.9%)	14 (9.5%)	85	1 (1.2%)	3 (3.5%)
EIAED	311	53 (17.0%)	34 (10.9%)	385	9 (2.3%)	21 (5.5%)
GLUAED	291	53 (18.2%)	18 (6.2%)	344	12 (3.5%)	12 (3.5%)
NEIAED	232	27 (11.6%)	27 (11.6%)	223	6 (2.7%)	15 (6.7%)
InhAED	85	25 (29.4%)	6 (7.1%)	79	2 (2.5%)	4 (5.1%)

AED categories differed in the frequencies of reports of seizure increase on hormonal contraception ($X^2 = 14.270$, df = 4, $p = 0.006$) but not on nonhormonal contraception. The frequency of reports of seizure decrease did not differ significantly among AED categories on either HC or NHC. Relative to the frequency of seizure increase reported by WWE for no AED on hormonal contraception (18.9%), the risk ratio (RR) for seizure increase on InhAED (29.4%) trended greater (RR = 1.55 (0.97–2.48), $p = 0.065$), whereas the RR for NEIAED (11.6%) was less (RR = 0.62 (0.38–1.00), $p = 0.05$). Relative to NEIAED, the category that had the lowest frequency of seizure increase on HC (11.6%), all of the other AED categories showed greater RRs for seizure increase: InhAED (RR = 2.53 (1.56–4.10), $p = 0.0002$), GluAED (RR = 1.57 (1.02–2.41), $p = 0.04$), and EIAED (RR = 1.46 (10.95–2.25), $p = 0.08$). NEIAED, the category which had the highest frequency of seizure decrease on HC (11.6%), had a RR that was almost twofold greater than for GluAED, which had the lowest frequency (6.2%) (RR = 1.89 (1.06–3.33), $p = 0.03$). Each AED category showed a greater frequency of seizure increase than decrease on HC except the non-enzyme-inducing AED category: no AED (RR = 2.00 (1.10–3.64), $p = .02$), enzyme-inducing AED (RR = 1.56 (1.04–2.33), $p = 0.03$), glucuronidated AED (RR = 2.80 (1.69–4.66), $p = 0.0001$), non-enzyme-inducing AED (RR = 1.00 (0.61–1.65), p = NS), and enzyme-inhibiting AED (RR = 4.17 (1.80–9.64), $p = 0.0009$). There was no significant difference for any AED category on NHC. Abbreviations: HC = systemic hormonal contraception, NHC = nonhormonal contraception, AED = antiepileptic drug, EIAED = enzyme-inducing AED, GluAED = glucuronidated AED [lamotrigine], NEIAED = non-EIAED, InhAED = enzyme-inhibiting AED [valproate]. Mixed categories are analyzed separately.

3.4. Predictors of seizure increase and decrease on various combinations of contraception and antiepileptic drug categories

Binary logistic regression analysis showed that contraception category ($p < 0.001$) and interaction between contraception and AED categories ($p < 0.001$) were significant predictors of seizure increase. Using barrier (the contraceptive category with the lowest rate at 3.0%) as referent, HC was the only category with a significantly greater probability (OR = 12.829 (95% CI: 6.713–24.518, $p = <0.001$)). This is consistent with the finding reported above and in Fig. 1 for the RRs for seizure increase. Each AED category showed a significant interaction with HC but not with any of the NHC categories. In comparison to the combination of barrier and no AED, probabilities for seizure increase were as follows: HC and enzyme-inhibiting AED (valproate) (OR = 9.046 (5.016–16.312), $p < 0.001$), HC and glucuronidated AED (lamotrigine) (OR = 4.572 (2.859–7.310), $p < 0.001$), HC and enzyme-inducing AEDs (OR = 4.051 (2.559–6.415), $p < 0.001$), and HC and non-enzyme-inducing AED (OR = 3.022 (1.764–5.179), $p < 0.001$).

Binary logistic regression also showed an interaction between contraception category and AED category as a predictive factor for seizure decrease ($p = 0.006$). Probabilities again were significant for interactions between AED categories and HC ($p < 0.01$) but not NHC categories. Probabilities for interaction between HC and AED categories relative to the barrier and no AED category were as follows: HC and non-enzyme-inducing AED (OR = 3.896 (1.762–8.618), $p = 0.001$), HC and enzyme-inducing AED (OR = 2.950 (1.384–6.286), $p = 0.005$), HC and glucuronidated AED (lamotrigine) (OR = 2.271 (0.994–5.191), $p = 0.052$), and HC and enzyme-inhibiting AED (valproate) (OR = 1.039 (0.225–4.790), $p = 0.961$).

4. Discussion

4.1. Differential effects of contraceptive methods on seizures

Although the majority of WWE in the EBCR report no change in seizure frequency with the use of any category of contraception, more WWE experience changes on HC than on NHC. The RRs for both seizure increase and decrease are greater with HC than NHC, with seizure increase predominating. On HC, the RR is greater with hormonal patch and progestin-only pills than with combined pills. The RR for seizure decrease is greater with depomedroxyprogesterone than with combined pills.

Despite the widespread use of HC, there is a paucity of evidence regarding the neuroactive properties of the synthetic steroid constituents of HC. With regard to ethinyl estradiol, one study on electroshock seizure thresholds in female rats found that, although synthetic progestins did not have a significant effect, coadministration with ethinyl estradiol significantly lowered the seizure threshold [20]. Another study found that the administration of ethinyl estradiol for 14 days to female mice lowered hippocampal-kindled seizure thresholds and increased seizure severity [21]. Ethinyl estradiol may also increase seizure severity in the baboon [22]. Whereas natural progesterone increases the serum and cerebral levels of allopregnanolone (a potent allosteric agonist of the $GABA_A$ receptor [8–12]) and shows efficacy (class III evidence) in the treatment of perimenstrually exacerbated seizures [23], synthetic progestins lower the serum and cerebral cortical levels of allopregnanolone, change $GABA_A$ receptor subunit expression, and produce anxiety-like behavior in a female rat model [24]. Synthetic progestins have not shown efficacy in seizure management except when used in dosages which result in amenorrhea [25].

There are reasons to consider that the differential effects of contraceptive categories on seizure frequency may reflect biological causes rather than just reporting bias. A biological effect of HC on seizures is

suggested by some significant differences among the subcategories of HC. Combined pills carried the lowest risk for seizure increase among HC subcategories. The highest risk occurred with the hormonal patch, the only subcategory which is known to produce substantially higher serum levels of ethinyl estradiol than combined pills [26,27]. Specifically, the patch produces 60% higher serum ethinyl estradiol levels than the 35-μg ethinyl estradiol-containing combined pills. Since ethinyl estradiol has proconvulsant properties [20–22], the higher ethinyl estradiol concentration produced by the patch may account for its significantly greater risk for seizure increase.

In contrast, depomedroxyprogesterone, known to reduce seizure frequency when used in dosages which produce amenorrhea [25], was associated with a substantially greater risk for seizure decrease than combined pills. Note, however, that depomedroxyprogesterone was associated with somewhat more reports of seizure increase than decrease (19% versus 17%). It remains to be determined whether the difference in directional response of seizures might be related to partial versus total suppression of ovarian estradiol secretion. For example, if estradiol has a proconvulsant effect [2–7], it is possible that the use of a standard regimen of depomedroxyprogesterone treatment might produce only partial estradiol suppression when used with an enzyme-inducing AED as compared to complete estradiol suppression when used with a non-enzyme-inducing AED, resulting in an increase in seizures with an enzyme-inducing AED yet a decrease with a non-enzyme-inducing AED. The current EBCR findings do not yet have enough statistical power to address this point conclusively. The importance of the level of estrogen suppression is also raised by the finding that the contraceptive progestin-only pills, which have low progestin content and exert contraceptive action more by the thickening of cervical mucus rather than by hormonal suppression, had greater RRs for seizure increase, not decrease, in comparison to combined pills. The EBCR did not obtain data regarding the progestin-only pill dosages used by participants and, therefore, cannot conclude whether the substantially higher dose progestin-only pills, which are used in the treatment of endometriosis and abnormal vaginal bleeding because they suppress ovarian steroid production, might differ in their effects on seizures and mimic depomedroxyprogesterone rather than the typical contraceptive progestin-only pills.

With regard to intrauterine device and tubal ligation, which had significantly higher frequencies of reports of seizure decrease than withdrawal which had the lowest frequency, 20 of 30 (66.7%) WWE who reported seizure decrease on intrauterine device and 5 of 6 (83.3%) WWE who reported seizure decrease on tubal ligation had also used HC. Since HC is associated with more reports of seizure increase than any other category, it is difficult to determine whether reports of seizure decrease on intrauterine device and tubal ligation represent an actual protective effect of these categories versus an improvement relative to seizure increase that WWE may have experienced with the use of HC. In favor of the latter explanation is the finding that among WWE on intrauterine device, 50% of the HC experiences were associated with reports of seizure increase as compared to only 18.7% on HC for WWE in the EBCR overall.

4.2. Differential impact of antiepileptic drugs on the contraceptive effects on seizures

The EBCR findings suggest that AED categories differ in their impact on the effects of HC on seizure frequency. An enzyme-inhibiting AED (valproate) may pose the highest risk and non-enzyme-inducing AED, the lowest risk for seizure increase on HC. Among combinations of AEDs, glucuronidated AED + enzyme-inhibiting AED, the two AED categories which have lower serum levels on active combined pills [14,28], likely because of the hepatic induction of glucuronidation by estrogen, may pose a higher risk than no AED on HC.

Seizure increase was significantly more likely to occur on each AED category in combination with HC than with NHC. On HC, the risk for seizure increase was greater for the enzyme-inhibiting category, specifically valproate, than for any other AED category. This finding is a potentially important clinical issue that requires further investigation and, if true, demonstration of a pathophysiological mechanism. Hormonal contraception lowers glucuronidated AED serum levels [14]. This has been demonstrated for valproate, as well as lamotrigine [28]. The lowering of AED levels, however, would not be an entirely adequate explanation since lamotrigine levels are found to drop more than valproate with HC [28], yet the rates of seizure increase with HC are greater when combined with valproate (29.4%) than with lamotrigine which had a rate very similar to no AED (18.2% versus 18.9%) in the EBCR population. Another consideration is that these AEDs may have differential effects on contraceptive hormone levels. Whereas lamotrigine has an insignificant lowering effect on ethinyl estradiol levels [19], might the enzyme-inhibiting valproate possibly raise ethinyl estradiol levels in women, resulting in a proconvulsant effect? There is, as yet, no conclusive evidence in WWE. One study of ethinyl estradiol levels on combined pills before and after introduction of valproate therapy in 6 healthy female controls reported higher peak and area-under-the-curve levels of ethinyl estradiol on valproate, but the difference was significant only for peak levels [29]. Of note, higher serum estradiol levels on valproate treatment have also been reported to occur in a study of men with epilepsy as compared to healthy controls [30]. Of course, the impact of valproate may relate to changes in the concentrations of other neuroactive steroids not under consideration here.

The non-enzyme-inducing AED category had the highest frequency of reports of seizure decrease. It had the highest and most significant probability for seizure decrease in comparison to other AED categories, relative to no AED on barrier. It was the only category that did not have a significantly greater frequency of seizure increase than decrease on HC, and seizure decrease was significantly greater than for glucuronidated AED. While the finding that the lowest frequency of reports of seizure decrease occurred on glucuronidated AED could be due to the induction of glucuronidation by ethinyl estradiol, we found no significant difference in the frequency of reports of seizure decrease between WWE on progestin-only pills as compared to combined pills at this juncture of the study. Likewise, although levetiracetam had a more favorable profile than zonisamide for both seizure increase and decrease, the differences were not significant.

4.3. Seizure safety of hormonal contraception for women with epilepsy

Although large-scale, community-based, epidemiological studies have been lacking, published reviews have stated that there is no evidence that oral contraceptives increase seizure activity [31,32]. While the EBCR retrospective survey results are consistent with this opinion as it pertains to the majority of WWE, the EBCR finds that HC is associated with a broader range of seizure responses than NHC. More specifically, a substantial minority of WWE may experience a change in seizure frequency with HC, either increase or decrease, with increase predominating. The HC outcome, moreover, may vary by AED category. On HC, non-enzyme-inducing AEDs had the most favorable profile and enzyme-inhibiting AED (valproate), the AED that historically has been listed among the AEDs that are appropriate to use with HC, the least. Although the methodology of ascertainment of data may contribute some level of bias to the EBCR findings [1], we present some plausible pathophysiological mechanisms by which HC and HC–AED interactions might impact seizure frequency. The EBCR findings suggest a need for prospective investigation of the impact of various AED categories on the differential effects of hormonal contraception on seizures.

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Conflict of interest

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