



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



Andrew G. Herzog^{a,*}, Hannah B. Mandle^a, Kaitlyn E. Cahill^a, Kristen M. Fowler^a, W. Allen Hauser^b

^a Harvard Neuroendocrine Unit, Beth Israel Deaconess Medical Center, Boston, MA, United States

^b Gertrude H. Sergievsky Center, Mailman School of Public Health, Columbia University, New York, NY, United States

ARTICLE INFO

Article history:

Received 9 March 2016

Revised 5 April 2016

Accepted 6 April 2016

Available online 17 May 2016

Keywords:

Contraception

Epilepsy

Seizures

Women

Epidemiology

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.

© 2016 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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

* Corresponding author at: Harvard Neuroendocrine Unit, Beth Israel Deaconess Medical Center, 422 Worcester Street, Suite 303, Wellesley, MA 02481, United States. Tel.: +1 781 431 0277; fax: +1 781 431 0274.

E-mail address: aherzog@bidmc.harvard.edu (A.G. Herzog).

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 \leq 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.

Download English Version:

<https://daneshyari.com/en/article/6009885>

Download Persian Version:

<https://daneshyari.com/article/6009885>

[Daneshyari.com](https://daneshyari.com)