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FPIN's Clinical Inquiries

Effect of Antiepileptic Drugs on Oral Contraceptives

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Clinical Question

Do antiepileptic drugs affect oral contraceptive effectiveness?

Evidence-Based Answer

We found no studies that measure, or even estimate, any increase in pregnancy rates in women taking antiepileptic drugs. Antiepileptic drugs known to induce the hepatic cytochrome P450 (CYP450) isoenzyme cause decreased sex hormone levels in women taking oral contraceptives, raising the potential for decreased effectiveness of oral contraceptives and increased risk of unplanned pregnancy. (Strength of Recommendation [SOR]: C, based on small cohort studies). Antiepileptic drugs that do not induce this hepatic isoenzyme are not thought to compromise the effectiveness of oral contraceptives. (SOR: C, based on small cohort studies and randomized controlled trials).

Evidence Summary

Antiepileptic drugs are being used more often for problems such as migraine headaches, chronic pain syndromes, and bipolar disorder. If antiepileptic drugs negatively affect oral contraceptive effectiveness, the potential for contraceptive failures increases as more women take antiepileptic drugs and oral contraceptives concurrently. Antiepileptic drugs that induce the hepatic CYP450 isoenzyme (called enzyme-inducing antiepileptic drugs) accelerate the conversion of estrogen and progesterone to inactive metabolites, thereby decreasing serum concentrations of hormones found in oral contraceptives. Some antiepileptic drugs may also increase sex hormone-binding globulin concentrations, which could affect oral contraceptive effectiveness by decreasing bioavailability of the active ingredients. The studies available did not examine pregnancy rates, but instead examined blood hormone levels or bleeding patterns.

ENZYME-INDUCING ANTIEPILEPTIC DRUGS

Phenobarbital is an enzyme-inducing antiepileptic drug that interacts with oral contraceptives, causing decreased sex hormone levels¹ and breakthrough bleeding.² Midcycle breakthrough bleeding signals an estrogen deficiency, with potential failure of contraception, and is thought to show evidence of decreased effectiveness of oral contraceptives. Phenytoin (Dilantin) also decreases serum hormone levels and allows breakthrough bleeding.^{2,3} Similar results have been found with carbamazepine (Tegretol),^{2,3} felbamate

(Felbatol),⁴ oxcarbazepine (Trileptal),^{5,6} and topiramate (Topamax).⁷

NONENZYME-INDUCING ANTIEPILEPTIC DRUGS

Valproic acid (Depakote) has no known interaction with oral contraceptives. In one observational study, four of six women actually had increased sex hormone levels while taking valproic acid.⁸

Benzodiazepines,² gabapentin (Neurontin),⁹ lamotrigine (Lamictal),^{10,11} levetiracetam (Keppra),^{12,13} tiagabine (Gabitril),¹⁴ and zonisamide (Zonegran)¹⁵ are also nonenzyme-inducing antiepileptic drugs that do not appear to interact with oral contraceptives. Formal studies of possible interactions between oral contraceptives and ethosuximide (Zarontin) have not been conducted; however, interactions are doubtful because ethosuximide is not known to cause hepatic enzyme induction. *Table 1* lists enzyme-inducing and nonenzyme-inducing antiepileptic drugs.

Table 1. Enzyme-Inducing and Nonenzyme-Inducing Antiepileptic Drugs

Enzyme-inducing	Nonenzyme-inducing
Carbamazepine (Tegretol)	Benzodiazepines
Felbamate (Felbatol)	Ethosuximide (Zarontin)
Oxcarbazepine (Trileptal)	Gabapentin (Neurontin)
Phenobarbital	Lamotrigine (Lamictal)
Phenytoin (Dilantin)	Levetiracetam (Keppra)
Topiramate (Topamax)	Tiagabine (Gabitril)
	Valproic acid (Depakote)
	Zonisamide (Zonegran)

Recommendations from Others

The American College of Obstetrics and Gynecologists (ACOG) states that, although there are no published data to support this recommendation, it seems prudent to use a 30- to 35-mcg rather than a 20- to 25-mcg estrogen-containing oral contraceptive in women taking enzyme-inducing antiepileptic drugs.¹⁶

The ACOG also recommends using condoms with oral contraceptives or using intrauterine devices in women taking enzyme-inducing antiepileptic drugs. In a consensus statement, the American Academy of Neurology (AAN) suggests using oral contraceptive formulations containing at least 50 mcg of estrogen in women taking enzyme-inducing antiepileptic drugs.¹⁷ The AAN also states that oral contraceptive effectiveness in women using enzyme-inducing antiepileptic drugs remains superior to barrier methods.

The World Health Organization advises against using combined oral contraceptive pills and progestin-only pills in women taking enzyme-inducing antiepileptic drugs unless a better contraceptive method is not available or not acceptable to the patient; however, injectable medroxyprogesterone (Depo-Provera) is still a recommended method.¹⁸

Clinical Commentary

In the family medicine setting where I practice, we see a fair number of women taking antiepileptic drugs for seizure disorders, migraines, various mood disorders, and chronic pain. Because it is thought that some anti-epileptic drugs may cause oral contraceptive failure, it seems prudent for physicians to counsel these patients on the risk of pregnancy. Despite the lack of pregnancy outcome data, the use of antiepileptic drugs in pregnant women does not come without risks. Older antiepileptic drugs are known teratogens and newer antiepileptic drugs lack human pregnancy reports. Any woman of childbearing age who is prescribed an antiepileptic drug, even if she is not taking oral contraceptives, should be counseled on the risk of fetal defects, and should be given folate supplementation to help prevent neural tube defects. I also recommend documenting that conversation.

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