Decreased efficacy of an etonogestrel implant in a woman on antiepileptic medications: a case report

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Abstract

Introduction: Many antiepileptic drugs decrease the efficacy of combined hormonal contraceptives due to their inducing effect on cytochrome P450 liver metabolism. Less is known about the pharmacokinetics and outcomes of concomitant use of the etonogestrel implant and hepatic enzyme-inducing medications. 

Case presentation: A 22-year-old Hispanic woman with a long-standing seizure disorder treated with carbamazepine for 9 years became pregnant after 25 months of etonogestrel implant use.

Conclusions: Hepatic enzyme-inducing drugs may reduce the efficacy of contraceptive implants. Contraceptive counseling for patients with medical co-morbidities requiring hepatic enzyme-inducing medications should include this information.

Introduction

Hormonal contraceptives and antiepileptic drugs (AEDs) interact at the level of the liver’s cytochrome P450 (CYP450) enzyme pathway. Estrogens and progestins are metabolized by CYP450 3A4 [1-3]. Many AEDs, such as phenytoin, phenobarbital, oxcarbazepine, topiramate and carbamazepine are inducers of CYP450 3A4 isoenzymes in the liver [1]. Hepatic enzyme-inducing medications accelerate the metabolism of estrogen and progestins, thereby decreasing the intensity and duration of their action [1,2]. This phenomenon is best studied in patients using combined oral contraceptives (COCs) [2]. Carbamazepine co-administration with COCs results in decreased levels of contraceptive steroids, increased breakthrough bleeding and permits ovulation [3]. In a recent review of contraceptive methods and AEDs, 28 out of 34 studies evaluated COCs, and only four studied the levonorgestrel (LNG) contraceptive implant, which is no longer available in the USA [2].

Less is known about the widely used etonogestrel (ETG) implant (IMPLANON®, Merck, Darmstadt, Germany). In healthy women, the ETG implant is 99.95% effective [4]. Manufacturer’s trials report six pregnancies during 20,648 cycles, with each conception occurring shortly before or within 2 weeks after implant removal [5]. Women on medications that induce liver enzymes were excluded from the study. The implant package insert states that the ETG implant is not recommended for women requiring chronic use of inducing AEDs [5].

There are no published studies examining the pharmacokinetics of AEDs with the contemporary ETG implant. In the only study exclusively evaluating the pharmacokinetics of the LNG implant (Norplant), epileptic women treated with phenytoin alone or in combination with another anticonvulsant ($n=6$) were compared to healthy controls ($n=10$) and significantly lower levels of plasma LNG were observed in the group treated with AEDs at 3 to 12 months [6]. Two women with epilepsy (22%) became pregnant during the study period [2,6]. There are only three case series/reports documenting current ETG implant failure in women using AEDs [7-9]. Two case series evaluate multiple causes of failure: 1) Bensouda-Grimaldi et al. [7] document two out of 39 failures in France occurring in women using AEDs [7]; and 2) Harrison-Woolrych and Hill [8] report eight out of greater than 200 unintended pregnancies occurring with ETG implant and AED use [8]. Only one previous case report has exclusively documented a pregnancy in an ETG implant user on AEDs; this occurred 18 months after insertion [9]. This patient received an intrauterine
device (IUD) following pregnancy termination due to the
recognized potential interaction between AEDs and the
implant [9].

We present a case in which a patient with a chronic
AED history became pregnant after 25 months while using
the ETG implant. She maintained the pregnancy, and had
an uncomplicated term delivery. She then received another
ETG implant postpartum at another institution.

**Case presentation**

A 22-year-old gravid 2, para 0101, Hispanic woman with
a long-standing history of a seizure disorder treated with
carbamazepine 200mg four times a day for 9 years pre-
sented for ETG implant removal upon discovering she
was pregnant. She suspected pregnancy secondary to late
menses and morning sickness. She had the implant
placed 25 months prior at the time of her LNG-intrauterine
system (Mirena®, Bayer HealthCare, Wayne, NJ, USA) re-
moval. She used the LNG-IUS for the preceding 30 months,
which was placed at a 6-week post-partum visit, and discon-
tinued it due to her partner's discomfort during intercourse
secondary to contact with the device strings. She had a pre-
pregnancy body mass index of 29.2. An intrauterine preg-
nancy was confirmed with transvaginal ultrasound. The
ETG implant was removed at that visit.

She was followed by maternal fetal medicine and neur-
ology throughout her pregnancy. She experienced an in-
crease in the number of seizures during her pregnancy,
and her carbamazepine dose was increased to 400mg three
times a day Her pregnancy was otherwise uncomplicated.

She delivered a healthy boy at 39 weeks, weighing
3.63kg (8lbs), by normal spontaneous vaginal delivery.
At her 6-week post-partum visit at another institution, a
second ETG implant was placed. There was no docu-
mentation of counseling regarding potential decreased
efficacy of the implant due to her concomitant AED use.
Despite the previous failure, she accepted another im-
plant. She has not returned to our system or the institu-
tion that placed the second implant.

**Discussion**

Patients who take medications that induce hepatic me-
tabolism present challenges to providers prescribing hor-
monal contraception. Reliable contraception is essential
for these women as many AEDs are teratogenic [1,3,10].
Studies have established significant decreases in COC ef-
ficacy in women taking AEDs [2] and increasing
COC doses to 50µg to overcome inducing effects of
AEDs has been suggested [1,3,8]. Less is known about
the pharmacokinetics of the ETG implant with hepatic
enzyme-inducing AEDs, and providers must be aware of
potential interactions. Certain AEDs are not inducers of
hepatic metabolism and are safe and effective in combination
with hormonal contraception. These include valproic acid,
vigabatrin, lamotrigine, gabapentin, tiagabine, levetiracetam,
zonisamide, ethosuximide, and benzodiazepines [1,2,10].

When possible, these medications should be used for
women with epilepsy who desire a full range of hormonal
contraception options.

Providers should be aware of and utilize the **WHO Medical Eligibility Criteria for Contraceptive Use (MEC)**.

In women using hepatic enzyme-inducing AEDs, the
MEC assigns a category 2 rating. (“Advantages generally
outweigh theoretical or proven risks” [4]), and includes a
clarifying comment: “Although the interaction of certain
anticonvulsants with POPs and ETG implants is not
harmful to women, it is likely to reduce the effectiveness
of POPs and ETG implants” (POPs, progestogen-only pill)
[4]. Long-term users of AEDs are specifically highlighted
as an at-risk population for decreased implant efficacy:
“Use of other contraceptives should be encouraged for
women who are long-term users of any of these drugs”
[4]. The failure of the ETG implant in our case report and
one other both occurred in women with long-standing
histories of treatment with inducing AEDs. Reliable
contraceptive options assigned a category 1 rating (“A
condition for which there is no restriction for the use of
the contraceptive method” [4]) for hepatic enzyme-
inducing AED users include LNG-IUD, copper IUD,
and depot medroxyprogesterone acetate [4].

Studies mirroring the pharmacokinetic work with hep-
atic enzyme-inducing AEDs and COCs are needed to
make evidence-based recommendations regarding the
safety and efficacy of ETG implants in women taking
these medications. Prior research investigating progestin
implant metabolism in women using hepatic enzyme-
inducing AEDs is limited by short study periods, a small
number of women under investigation (N<20), incom-
plete information regarding AED type and dose, and its
focus on an implant that is no longer available in the USA
[2,6]. Pharmacokinetic and clinical trials are needed to
quantify the effect of AEDs on ETG implant metabolism.

Until this evidence is available, it is prudent for patients
and physicians to be aware of the potential interaction be-
tween the ETG implant and hepatic enzyme-inducing med-
ications. In our case, the placement of a second implant
despite its primary failure demonstrates a profound lack of
awareness among providers. Although this issue is ad-
dressed in the Federal Drug Administration (FDA)-required
training session for the ETG implant, providers are unlikely
to retain all information distributed at these sessions.

Further attention to this topic is needed in the literature.

**Conclusions**

Medically complicated patients must receive focused
contraceptive counseling regarding theoretical and known
drug interactions. When determining individual method
choice, ETG implants can be considered for women using
hepatic enzyme-inducing AEDs if the risks and benefits are adequately addressed. With 99.95% efficacy, the implant is significantly more effective than other methods in women not using AEDs [4]. Until pharmacokinetic studies are performed that quantify the actual reduction in efficacy among these patients, patients can be counseled that efficacy may be decreased, but is still likely to be higher than barrier methods, progestin-only pills, and COCs. High-efficacy contraceptive alternatives, or AEDs that do not interact with hepatic metabolism, should be considered.

Consent
Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations
AEDs: Antiepileptic drugs; COCs: Combined oral contraceptives; CYP450: Cytochrome P450; ETG: Etonogestrel; IUD: Intrauterine device; IUS: Intrauterine system; LNG: Levonorgestrel; MEC: WHO Eligibility Criteria for Contraceptive Use; POPs: Progestogen-only pills.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
JL performed the literature review, draft writing and editing, as well as manuscript submission and revision. ST contributed to idea conception as well as editing manuscript drafts. KT contributed to idea conception and execution, draft writing, and was a major contributor to manuscript editing. All authors read and approved the final manuscript.

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