

Medications That Interact With Contraceptives: Examining the Evidence

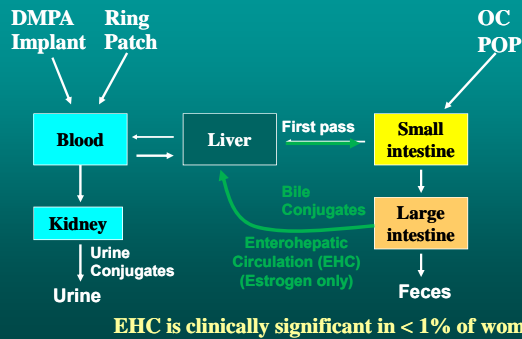
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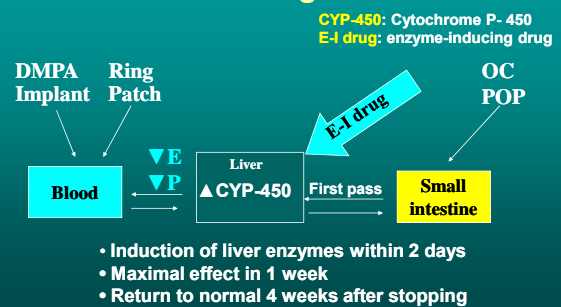
What Does the Evidence Say?

- In hormonal contraceptive (HC) users taking other drugs
- There are a few *case reports* of pregnancies
 - Many studies evaluate the effect of a challenge drug on *hormone levels* and breakthrough bleeding
 - Most of these with OC users
 - Very few studies of drug effects on *ovulation*
 - Virtually no studies of *pregnancy rates*...why?
 - Pregnancy is a rare event
 - RCTs are difficult; observational studies open to bias
 - Little incentive to fund these trials

Primary Metabolism of Steroid Drugs



Secondary Metabolism of Steroid Drugs



Effect of E-I Drugs on Pregnancy Risk

- How long the drug is taken
- The dose of the drug
- The route by which the drug is (primarily) metabolized
- The effect of the drug on induction of liver enzymes (secondary metabolism)
- The effect of liver enzymes on E + P metabolism and free hormone levels in the bloodstream
- The effect of lowered free E + P levels on the
 - Hypothalamic –pituitary–ovarian axis (ovulation)
 - Endometrium
 - Cervical mucus

Problems with Analysis of Existing Studies

- Most use hormone levels as a *surrogate marker* for ovulation, not ovulation rates or pregnancy rates
- Reductions in E + P presented as equally hazardous
- Findings in OC users extrapolated to *all types of HC*, even if no hepatic first pass effect
- External validity: limited findings in small groups of women often applied to *individual* women
- Overestimation of pregnancy risk if findings in a tiny subset of women are applied to all HC users

Urban Legend

- In women using hormonal contraceptives, the addition of a (non enzyme-inducing) antibiotic will increase BTB, ovulation, and pregnancy risk

The Reality

- There is *no evidence* that antibiotics will...
 - Reduce E+P in a clinically significant way
 - Increase pregnancy rates

Antibiotics in OC Users

- Based upon good quality studies, these antibiotics *do not* decrease steroid levels in women using OCs
 - Ampicillin
 - Clarithromycin
 - Metronidazole
 - Quinolone antibiotics (ciprofloxacin, ofloxacin)
 - Doxycycline, tetracycline

Long Term Antibiotics & OC Use

Helms SE, J Am Acad Dermol 1997;36: 705

- Retrospective, non-randomized; 3 derm practices
- Combination (abx + OC) used for at least 3 months
- No difference in BTB, diarrhea in women with OC failure (pregnancy) vs. OC success
- Findings

	n	Pregnancies/ woman yr	Preg/ HWY
OC+ antibiotic	356	5/311	1.6
OCs only	425	12/1,245	0.96

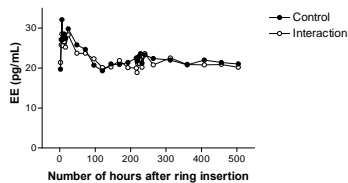
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Oral Antibiotics in OC Users

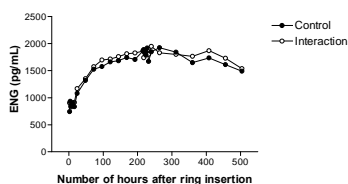
- By inhibiting bacteria in the colon, enterohepatic circulation of estrogen may be reduced in an extremely small subset (< 1%) of women...or not!!
- In small studies of OC users challenged by antibiotics, E+P levels do not drop significantly
- Long term users of antibiotics + OCs do not have higher pregnancy rates than those using OCs alone
- *In the absence of pharmacokinetic, observational, or epidemiologic data, it is no longer accepted that an interaction between antibiotics and OCs exists*

NuvaRing® With Doxycycline

No effect on ethinyl estradiol levels



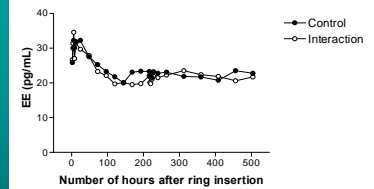
No effect on etonogestrel levels



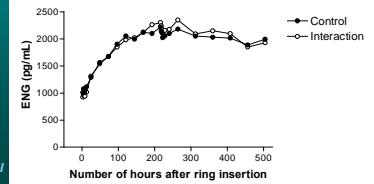
Dogterom and van den Heuvel

NuvaRing® With Amoxicillin

No effect on ethinyl estradiol levels



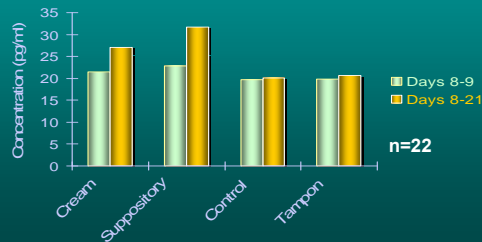
No effect on etonogestrel levels



Dogterom and van den Heuvel

NuvaRing® With Concomitant Anti-mycotic or Tampon Use

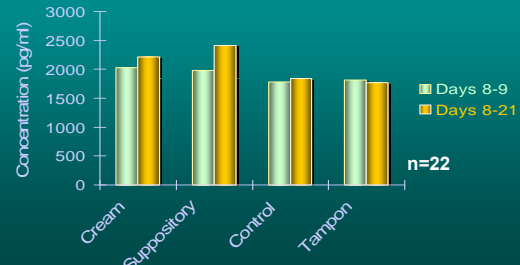
Ethinyl Estradiol



Haring & Mulders, Contraception 2004

NuvaRing® With Concomitant Anti-mycotic or Tampon Use

Etonogestrel



Haring & Mulders, Contraception 2004

Recommendations: Antibiotic Use in Hormonal Contraceptive Users

- In HC users taking a short or long course of antibiotics, there is **no evidence-based reason** to routinely recommend
 - Back-up contraception
 - A change to a more effective method
- If a woman is informed of a potential interaction, the **extremely low** magnitude of risk must be stressed
- Pregnancies that occur in women using both HC and antibiotics are due to other factors

Red Flag Conditions

- Seizure disorder/ epilepsy
- Tuberculosis
- Skin and nail fungal infections
- Depression
- HIV infection



Seizure Disorders

- Goals in contraceptive management of women with seizure disorders
 - Seizure control with anti-epileptic drugs (AEDs)
 - Highly effective contraception, as exposure to some AEDs is associated with congenital anomalies
 - Minimize interaction of AEDs and contraceptive
- **Enzyme inducing** AEDs reduce HC efficacy by
 - ▲ “secondary metabolism” of both E + P by induction of CYP450 (3A4) enzymes
 - ▲ SHBG ▼ free progestin (less with EE)

Urban Legend #2

- Estrogen in CHC causes inhibition of ovulation
- Low E causes BTB, which may be a sign of impending ovulation

The Reality

- The **progestin** in CHC inhibits ovulation by suppression of LH
- There is **no** evidence that BTB in women using CHC is a sign of ovulation, signaling that contraceptive failure is more likely

AEDs: Non Inducers of Hepatic Enzymes

Generic name	Brand name
Ethosuximide	Zarontin
Levetiracetam	Keppra
Tiagabine	Gabitril
Valproic acid	Depakene, Depakote
Vigabatrin	Sabril
Zonisamide	Zonegran
Clonazepam	Klonopin
Pregabalin	Lyrica



Enzyme Inducing Anti-Epileptic Drugs (AEDs)

Drug	Brand name	E reduction	P reduction
Carbamazepine	Tegretol ®	42%	58%
Felbamate	Felbatol ®	13%	42%
Lamotrigine	Lamictal ®	None	19%
Oxcarbazine	Trileptal®	48%	32%
Phenobarbital	generic	64-72%	None
Phenytoin	Dilantin ®	49%	42%
Topiramate	Topamax ®	15-33%	None

Thornycroft I, Epilepsy and Behavior 2006;9:31

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Thornycroft I, Epilepsy and Behavior 2006;9:31

Other Uses of EI-AEDs

Drug	Brand name	Common Other Uses
Carbamazepine	Tegretol ® Equetro ®	Trigeminal neuralgia, schizophrenia, bipolar disorder
Felbamate	Felbatol ®	Neuropathic pain, migraines
Lamotrigine	Lamictal ®	Bipolar, PTSD
Oxcarbazine	Trileptal®	Bipolar, neuropathic pain
Phenobarbital	generic	None
Phenytoin	Dilantin ®	None
Topiramate	Topamax ®	Migraines, bipolar, obesity



Management of Women Using EI-AEDs

- Ideal contraceptives
 - IUCs (Mirena, ParaGard)
 - DMPA: high efficacy; improves seizure control
 - Unknown if DP-104 reduces seizure activity
- Oral contraceptives...non-evidence based
 - Use at least 35 mcg EE + high progestin product
 - Shorten hormone free interval to 4 days or less
- Avoid “low progestin” contraceptives
 - OrthoEvra patch; progestin only pills

Thornycroft I, Epilepsy and Behavior 2006;9:31



Lamotrigine (Lamictal)

- Each drug increases the metabolism of the other
- In a Lamotrigine user started on OCs
 - Lamotrigine levels drop by 49% (41-64%)
 - Seizure activity increases
 - Side effects of lamotrigine ▲ when OC stopped
- If using OCs, use higher start dose of Lamotrigine
- If using Lamotrigine and initiating OCs
 - Double Lamotrigine dose *before* starting OCs
 - Before stopping OCs, cut Lamotrigine dose by half

Tuberculosis Drugs

- Enzyme inducers: Rifampin and Rifapentine (Priftin®)
 - First cases of OC failure due to 2nd drug (1971)
 - “Potent” CYP450 inducer + increases SHBG
 - Studies show ▼E, ▼P levels; 0-50% ovulate!!
- Other rifampin brand names
 - Rifadin®, Rimactane®, Rifamate® (Rifampin + INH)
 - Rifater® (Rifampin + INH + Pyrazinamide)
- Other “first line” drugs for TB: no HC interaction
 - INH (isoniazid), Pyrazinamide, Ethambutol
- Clinical recommendation
 - As for E-I AEDs; IUC or DMPA preferred

Rifampin and MRSA

- Rifampin now used widely for methicillin-resistant *Staph aureus* (MRSA) skin infections
- Rifampin should never be used alone for MRSA
 - Rapid emergence of resistant organisms
 - Poor efficacy against staph when used alone
- Concerns with enzyme-induction and (hormonal) drug interactions same as for TB treatment
- If rifampin Rx added to hormonal contraception
 - Short term: use back-up contraception
 - Long term: as suggested for E-I AEDs

Skin and Nail Fungal Infections

- Griseofulvin is used to treat
 - Dermatophytoses (ringworm); nail infections
 - Being replaced with newer oral antifungals
- Known to “induce hepatic enzymes”, but only a few case reports of pregnancy in 1980’s literature
- Antifungal drugs with no HC-drug interaction
 - Fluconazole, Itraconazole, Ketoconazole
- Clinical recommendation
 - Insufficient data!!!

St John’s Wort

- St John’s Wort widely used for depression
- Many studies show induction of CYP450 (3A4)
 - “Comparable to rifampin and carbamazepine when given for ≥10 days” (Markowitz, NEJM 2003)
- Studies of SJW in OC users

Study	Hormone level	ovulation	Follicle growth
Hall 2003	P, E ▼	no	NA
Pfrunder 2003	P ▼42%	no	no
Murphy 2006	P ▼15%	probable 38%	yes

▪ “Caution patients that OC effectiveness may be reduced”

Depression and Bipolar Disorder

- Depression
 - Possible effect: St John’s Wort
 - No effect
 - SSRIs (fluoxetine), SNRIs (venlafaxine)
 - Tricyclics (imipramine, amitryptiline)
- Bipolar Disorder
 - E-I AEDS
 - Carbamazepine, Oxcarbazine, Lamotrigine, Topiramate
 - No effect
 - Lithium, Aripiprazole (Abilify), Valproate

HIV Infection

Table 1. Pharmacokinetic Combination Oral Contraceptive-Antiretroviral Drug Interactions

Antiretroviral Levels	Contraceptive Steroid Levels	Antiretroviral
<i>Protease inhibitors</i>		
Nelfinavir	↓	No data
Ritonavir	↓	No data
Lopinavir/ritonavir	↓	No data
Atazanavir	↑	No data
Amprenavir	↑	↓
Indinavir	↑	No data
Saquinavir	No data	No change
<i>Nucleoside reverse transcriptase inhibitors</i>		
Nevirapine	↓	No change
Efavirenz	↑	No change
Delavirdine	?↑	No data

World Health Organization. Medical eligibility criteria for contraceptive use. Arnes. 1. COCs and antiretroviral therapy. 3rd ed. Geneva: WHO, 2004.

- Data from a few small unpublished studies show that OC metabolism may be altered when using ARVs
- No studies of clinical effect
- No clinical recommendations
- Stay tuned!!
- For HIV patients with MAC or TB, rifabutin induces liver enzymes, but < rifampin



Yasmin, YAZ and Potassium Levels

- 3 mg drospirenone has antiminerlocorticoid activity
 - Potential for hyperkalemia in *high-risk patients*, equal to 25-mg dose of spironolactone (100 mg is usual dose)
- If receiving *daily, long-term* drug treatment, check serum K levels during the first OC cycle
 - ACE inhibitors
 - Angiotensin-II receptor antagonists
 - Potassium-sparing diuretics
 - Aldosterone antagonists
 - Heparin
 - NSAIDs



Oral Contraceptives: Fair Data

- **Enzyme-inducing Anti-Epileptic Drugs (AED)**
 - Reduce progestin level, which may permit ovulation
 - Reduce estrogen level, which may cause BTB
 - May fail more often in *some* women
- **Rifampin, St John's Wort**
 - May have E-I effect to same magnitude as AEDs
- **Griseofulvin**
 - Has an uncertain impact on enzyme induction
- **Other non enzyme-inducing drugs**
 - Have no effect on hormone levels, OC efficacy

Findings Extrapolated from OCs

Hormonal contraceptive	Studies with anti-epileptic drugs	
Progestin only pills	None	
OrthoEvra	None	
Nuva Ring	None	
Implanon	None	

Findings Extrapolated from OCs

Hormonal contraceptive	Studies with anti-epileptic drugs	Studies with antibiotics
Progestin only pills	None	None
OrthoEvra	None	None
Nuva Ring	None	No effect of amoxicillin, doxycycline, antifungal
Implanon	8 case reports: carbamazepine	None



Good Data Showing No Effect

- DMPA (DepoProvera)
 - 100% first pass liver metabolism; not affected increased liver enzymes
- LN-IUS (Mirena)
 - Local effect of LN on endometrium is not affected by increased liver enzymes
- Cu-IUC (ParaGard)
- Barrier methods
 - Mechanisms of action not affected by drugs

2004 WHO Medical Eligibility Criteria

Drug	OC	P/R	POP	DMPA	Imp-lant	C-IUC	LN-IUC
Rifampin (E-I)	3	2	3	2	3	1	1
E-I Anticonvulsants	3	2	3	2	3	1	1
Griseofulvin	2	1	2	1	2	1	1
Other antibiotics	1	1	1	1	1	1	1
Anti-retrovirals	2	2	2	2	2	I 2/3	C 2/3

2004 WHO Medical Eligibility Criteria

Drug	OC	P/R	POP	DMPA	Implant	C-IUC	LN-IUC
Rifampin (E-I)	3	2	3	2	3	1	1
E-I Anticonvulsants	3	2	3	2	3	1	1
Griseofulvin	2	1	2	1	2	1	1
Other antibiotics	1	1	1	1	1	1	1
Anti-retrovirals	2	2	2	2	2	I 2/3	C 2 2/3 2

Take-Home Messages

- In addition to drug history, use the patient's *medical condition* as a "red flag" for drug interactions
- As needed, confer with PCP or neurologist to co-manage women using enzyme inducing AEDs
- With E-I drugs, ▼ progestin is more critical than ▼ estrogen in maintaining method efficacy
- When using antibiotics, *do not* routinely recommend method modifications, as any change in routine may *increase* the risk of pregnancy

References

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