

FSRH CEU Statement: Response to Recent Publication Aronson and Ferner, 2020

“Analysis of reports of unintended pregnancies associated with the combined use of non-enzyme inducing antibiotics and hormonal contraceptives”

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Why is this statement necessary?

Since oral contraception first became available, there have been concerns that antibiotics might interfere with their efficacy. There is limited published evidence to inform this issue; however, most data for non-enzyme inducing antibiotics have been reassuring. The journal *BMJ Evidence Based Medicine* recently published a study¹—which has received some media attention—suggesting that concomitant use of non-enzyme inducing antibiotics could reduce the effectiveness of “hormonal contraceptives”.

Aronson and Ferner¹ reviewed Yellow Card reports to the UK’s Medicines and Healthcare Products Regulatory Agency (MHRA) between 1963 and July 2018. They compared the number of unintended pregnancies reported spontaneously as suspected adverse drug reactions (ADRs) in women of any age during use of medications in one of three groups:

- ▶ Commonly used non-enzyme-inducing antibiotics (74,623 ADRs reported)
- ▶ Hepatic enzyme-inducing medications known to interact with some hormonal contraceptives (32,872 ADRs reported)
- ▶ ‘Control’ medications commonly used by reproductive-age women and not known to impact efficacy of hormonal contraceptives (65,578 ADRs reported)

It is important to note that the authors did not report any information on the demographics of the women included in the study, including whether they were of childbearing age, or using contraception. Furthermore, the authors assumed that, if an unintended pregnancy was reported as a suspected adverse effect of a drug, the individual must have been using contraception with which the drug could have interacted.

What were the study findings?

Over the 55 years of data, 46 unintended pregnancies were reported as ADRs involving non-enzyme inducing antibiotics (this equates to 0.84 per year in the entire UK population). 39 were reported for enzyme-inducing medications and 6 for control medications. Although no meaningful denominators were available, the study authors calculated the rate of reported unintended pregnancies per total number of reported ADRs for each medication category. For every 100,000 reported ADRs involving non-enzyme inducing antibiotics, 62 were pregnancies. For enzyme-inducing medications 119 of every 100,000 reported ADRs were unintended pregnancies, and for control medications, 9.

Comparing these rates, the study authors reported that unintended pregnancies were 7 times more common among reported ADRs for non-enzyme inducing antibiotics compared to control medications and inferred that the “7-fold higher rate of reported unintended pregnancies with antibiotics” constituted a signal of possible drug-drug interaction. The authors concluded that non-enzyme inducing antibiotics may impair the effectiveness of (hormonal) contraceptives and that extra contraceptive precautions are needed during a short course of non-enzyme inducing antibiotics.

Limitations of this study

This study has significant shortcomings that severely limit the conclusions that can be drawn from it and its applicability to clinical practice, as also noted in correspondence published in response to the paper².

First, the authors do not know what (if any) method of contraception was being used by any of the individuals that reported ADRs. They cannot, therefore, say how many of the reported unintended pregnancies in any of the medication groups that they analysed were due to contraceptive failure. However they make the assumption that all Yellow Cards reporting unintended pregnancy related to hormonal contraceptive users, discounting individuals potentially using no or non-hormonal contraception. They state: “[a]lthough we do not know that the reports of unintended pregnancies all concerned women who were taking hormonal contraceptives, it is highly unlikely that anyone would report an unintended pregnancy to the MHRA on a Yellow Card, the purpose of which is to record suspected adverse drug reactions, if the pregnancy was not thought to be due to failure of hormonal contraception.” Basing their conclusion on such a large assumption significantly limits the interpretability of their data.

Thus, this paper compares the proportion of ADRs that were unintended pregnancies in women using non-enzyme inducing antibiotics, enzyme-inducers, and a selection of medications commonly taken in women of child-bearing age, but **not** the proportion of ADRs that were unintended pregnancies among women using a hormonal contraceptive and each of these three medication groups.

Secondly, this analysis is entirely based on voluntary reporting of suspected ADRs via the Yellow Card scheme, which may well be subject to reporting bias. As the authors acknowledge, many healthcare providers suspect that there are drug interactions between hormonal contraception and antibiotics, despite the lack of definitive evidence. As a result, healthcare providers and patients may be more likely to submit a Yellow Card report when a pregnancy occurs in a woman using an antibiotic compared with one of the control medications. They may not report a contraceptive failure during use of an enzyme inducer because it is an expected event. Furthermore, the dataset contains no comprehensive denominators (i.e. the total number of women taking hormonal contraception who have taken antibiotics or any of the control medications, and for what time period) or numerators (i.e. the total number of unintended pregnancies among women taking hormonal contraception), making calculation of meaningful rates for comparison across groups impossible. The rate of unintended pregnancy reported among all reported ADRs may be influenced markedly by the overall adverse event profile of a medication, rendering this metric inappropriate for the type of comparisons presented in the paper.

Thirdly, we cannot assume that the non-enzyme inducing antibiotic, enzyme-inducing, and control medication groups have equivalent baseline risk for unintended pregnancy, which may confound the comparisons being made, leading to spurious associations. For example, in the non-enzyme inducing antibiotic group, metronidazole and nitrofurantoin are more commonly used in younger, sexually active women, the population at highest risk of unintended pregnancies. In contrast, the control medication group includes medications such as theophylline and propranolol, used used for treatment of respiratory and cardiac conditions more common among older women, who may be at lesser risk for pregnancy. Without any socio-demographic information about these comparison groups (e.g. age, socioeconomic status, medical history), we cannot make the assumption that the groups have equivalent baseline risk for unintended pregnancies². It is unclear why the authors did not limit their analysis to women of childbearing age, as these data are available in the MHRA Yellow Card data repository.

Finally, the authors propose possible mechanisms for a potential drug interaction between (oral) contraceptives and non-enzyme inducing antibiotics, with a focus on how such an interaction affects estrogen levels in oral contraceptives. Pharmacologically, the progestogen component of combined oral contraceptives provides the main contraceptive effect³. Unlike estrogens, progestogens do not rely on enterohepatic recirculation, and thus, antibiotic-induced gastrointestinal changes would not affect the efficacy of these progestogens³⁻⁵. Just to reiterate, we do not know what (if any) contraceptive method was being used at the time of the unintended pregnancies reported by this study.

What is the current guidance?

After systematically reviewing all published evidence on this topic, the US Center for Disease Control and Prevention⁶, the World Health Organization, and the Faculty of Sexual & Reproductive Healthcare's Clinical Effectiveness Unit (FSRH CEU)⁷ have concluded on multiple occasions (2009, 2010, 2015, 2017) that common non-enzyme-inducing antibiotics do not impair the effectiveness of hormonal contraception, including combined oral contraceptives, patches, or rings and that extra precautions are not required when antibiotics are prescribed.

How does this study affect FSRH guidance?

- ▶ Given its substantial limitations, the findings from the Aronson and Ferner (2020) study are not scientifically robust enough to warrant any change to FSRH CEU guidance.
- ▶ FSRH CEU guidance remains that additional contraceptive precautions are not required when antibiotics are prescribed to users of hormonal contraception⁶.
- ▶ In women using known enzyme-inducing medications long-term, including enzyme inducing antibiotics, the FSRH CEU recommends intrauterine contraception (IUC) or injectable contraception (DMPA)⁷.

References

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