

Absence of Proof Is Not Proof of Absence

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Recently, interest has been renewed in the purported interaction between oral contraceptives (OCs) and antibiotics. It has been almost 40 years since this interaction was first reported to increase the risk of unintended pregnancy, and yet the interaction still generates much debate. Unfortunately, the existence or absence of this interaction still cannot be established based on the currently available scientific data.

Most drug interactions have areas of uncertainty, but we still must make decisions based on this incomplete information. As philosopher John Locke observed, “It is not possible to achieve certainty in our knowledge of the empirical world, but we can devise workable approximations and act on them.” Here are a few suggestions for making sense of the debate on the OC–antibiotic interaction.

Study the Original Data

If one plans to assess any drug interaction and publish the conclusions for others to use in making decisions, one must read the published data. Because the literature on the OC–antibiotic interaction now exceeds 200 articles, few people who make proclamations on this interaction in print have actually read all the data. It is risky to publish a conclusion based on reading only reviews or (worse) uncritically relying on what “authorities” say (including the authors of this column!).

Of course, every pharmacist cannot read all of the original data on the thousands of reported drug interactions, so

he or she has no choice but to rely on the evaluations of experts. It is important to rely on expert opinion, however, that is based on a critical evaluation of the scientific data.

Objectivity

Cognitive scientists know that humans often unconsciously ignore information that is contrary to their prejudices. Therefore, if one has decided ahead of time that the OC–antibiotic interaction probably is (or is not) real, it will be difficult for them to read the data objectively. One must make every effort to remain agnostic as to the results of his or her inquiry. Philosopher Simon Blackburn called *objectivity* the “cardinal virtue of reasoning.”

Why Is There Still Debate About This Interaction?

1. *No definitive study has been done.*

Even if an OC–antibiotic interaction occurs, it is probably rare; hence, a large epidemiologic study of just certain antibiotics (see number 2 below) would be required to detect an interaction. Many studies have involved small numbers of subjects, virtually eliminating any chance of finding an interaction. Similarly, anecdotal case reports—although large in number—do not establish that an interaction *does* occur.

2. *Failure to consider differences in antibiotics.*

Rifampin is a potent enzyme inducer that increases the risk of contraceptive failure by increasing the metabolism of OCs. Griseofulvin, nafcillin, and dicloxacillin probably have a similar (if less marked) effect. On the other hand, drugs like clarithromycin, erythromycin, quinupristin, and telithromycin

are cytochrome P450 3A4 (CYP3A4) inhibitors, and theoretically would *increase* the circulating concentrations of OCs. Many other antibiotics studied in combination with OCs have varying effects on CYP450 isozymes, intestinal flora, and intestinal motility; nonetheless, several frequently cited studies looked at the effects of “antibiotics” as a group on OC failure.

3. *Infection vs antibiotic.* Little is known about the effect of an infection itself on contraceptive failure. Infection-related vomiting or diarrhea theoretically could reduce OC absorption, and women who are ill might be more likely to miss OC doses. Women with infections might also be less likely to have sexual intercourse, thus masking a possible effect of antibiotics on OC efficacy in published studies. These theoretical possibilities have not been carefully studied.

Summary

Specific antibiotics may or may not increase OC failure, but to assume the interaction has been “debunked” or “disproved” is not consistent with the data. Taken as a whole, the data are consistent with either (1) no interaction, or (2) a rare interaction that occurs only in certain predisposed women taking a particular OC with a particular antibiotic. If the interaction is removed from future OC labels, legal liability may be reduced. Nonetheless, until we have a definitive negative study, it would be prudent to advise patients about the controversy (no matter which antibiotic is involved), and let them decide if they wish to take extra contraceptive precautions against pregnancy during and for at least 7 days (preferably the rest of the cycle) after the antibiotic is finished. ■