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# Drug interactions between rifamycin antibiotics and hormonal contraception: a systematic review

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## Abstract

**Background—**Rifamycin antibiotics are commonly used for treatment of tuberculosis, but may reduce the effectiveness of hormonal contraception (HC).

**Objectives—**To determine whether interactions between rifamycins and HC result in decreased effectiveness or increased toxicity of either therapy.

**Search strategy—**We searched MEDLINE, Embase, Cochrane and clinicaltrials.gov through May 2017.

**Selection criteria—**We included trials, cohort, and case-control studies addressing pregnancy rates, pharmacodynamics or pharmacokinetic (PK) outcomes when HC and rifamycins were administered together versus apart. Of 7291 original records identified, 11 met inclusion criteria after independent review by two authors.

**Data collection and analysis—**Two authors independently abstracted study details and assessed study quality using the United States Preventive Services Task Force grading system. Findings are reported descriptively.

**Main results—**Studies only addressed combined oral contraceptives (COCs) and none reported pregnancy rates. Quality ranged from good to poor. Rifampin increased the frequency of ovulation in two of four studies, and reduced estrogen and/or progestin exposure in five studies. Rifabutin

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Contributions to authorship

Dr Simmons performed the initial search, abstract and full text review, data abstraction, study grading, and wrote the manuscript. Drs Haddad, Nanda, and Curtis performed review of full texts, data abstraction, study grading, and critically reviewed the manuscript. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Details of ethics approval

No ethics approval was required for this systematic review.

led to smaller PK changes than rifampin in two studies. In one study each, rifaximin and rifalazil did not alter hormone PK.

**Conclusions—**No studies evaluated pregnancy risk or non-oral HCs. PK and ovulation outcomes support a clinically concerning drug interaction between COCs and rifampin, and to a lesser extent rifabutin. Data are limited for other rifamycins.

## Tweetable abstract

Rifampin and rifabutin reduce systemic exposure of oral contraceptives, but no studies have evaluated pregnancy risk.

### Keywords

antibiotics; contraceptive effectiveness; contraceptive failure; drug exposure; drug interactions hormonal contraception; ovulation; rifabutin; rifampin; rifamycins; tuberculosis

## Introduction

Approximately 10.4 million people developed new tuberculosis (TB) disease in 2015, including 3.5 million women.[1] The recommended treatment for new cases of drug-susceptible TB remains a 6-month regimen of rifampin, isoniazid, pyrazinamide and ethambutol.[1,2] Additional rifamycin regimens are either already in use or are in clinical trials for treatment of TB, including rifapentine, rifabutin, and high-dose rifampin.[1,2] To achieve the United Nations (UN) Sustainable Development Goal of ending the global TB epidemic by 2030, use of this drug class will remain widespread among women of reproductive age. It is therefore critical to understand how these drugs might affect another UN Sustainable Development Goal: universal family planning services.[3]

Millions of women worldwide use hormonal contraception (HC) to achieve their desired family size or to prevent unintended pregnancies, including many in TB-prevalent areas.[4] Clinical reports have implicated rifampin with combined oral contraceptive (COC) failure since the 1970s.[5] Multiple mechanisms may account for increased COC failure with rifampin use. Rifampin induces hepatic cytochrome P450 (CYP) enzymes required for COC metabolism, which could result in a reduction of systemic levels of contraceptive steroid hormones.[6] It also leads to increased production of the hepatic protein sex hormone-binding globulin, which binds circulating progestins and reduces biologically active progestin exposure.[5] Clinical guidance from the World Health Organization (WHO) generally advises against the concurrent use of rifampin or rifabutin with COCs, patches or rings given the theoretical risk for reduced contraceptive effectiveness.[7] However, clinical data are limited, and other rifamycins in clinical use and in development have different pharmacokinetic properties, including rifapentine, rifabutin, rifaximin and rifalazil.[8] Less is known about the interaction of these other drugs with HC. Likewise, little is known about the interaction of rifamycins on non-oral formulations of HC. Given current global efforts to eradicate TB, it is imperative for healthcare providers to understand how TB therapy can affect HC, and thereby help women avoid an undesired or unplanned pregnancy during treatment. Similarly,

TB treatment providers should be aware of any potential for altered clinical efficacy of TB therapies with concomitant use of HC.

The objective of this systematic review is to evaluate published literature on the interaction between rifamycin antibiotics and HC. Specifically, we addressed the research question: among women taking HC or rifamycins, do users taking these drugs together experience decreased contraceptive or antibiotic effectiveness, or increased hormonal or antibiotic toxicity, compared with users taking each drug alone?

## Methods

We developed a systematic review protocol containing pre-specified exposures, outcomes, eligibility criteria, search terms, and study grading criteria. We report this systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[9]

### Types of studies and exclusion criteria

We included clinical trials (randomised and nonrandomised), cohort, case-control, and pharmacokinetic (PK) studies, and excluded abstracts, case reports, case series, cross-sectional studies, letters, editorials, review articles without primary data, and non-published results. We required that all included studies have a comparison group, and therefore also excluded prospective observational studies without a control group. We included studies of any method of HC in combination with any rifamycin, but excluded studies of non-contraceptive formulations of steroid hormones (IV estrogen). Our clinical outcomes included pregnancy, presumed ovulation by serum progesterone with or without ultrasound, TB disease progression or TB-related death, and adverse health effects (breakthrough bleeding, drug side effects or adverse events). We included PK studies of either the contraceptive steroid hormone or the rifamycin drug that reported area under the curve (AUC), maximum serum concentration (Cmax), minimum serum concentration (Cmin) or mean 24-hour drug levels, and excluded studies only reporting steroid hormone urinary excretion.

### Types of participants

We included studies of women with or without TB.

### Search strategy

We searched MEDLINE, Embase, Clinicaltrials.gov, and Cochrane libraries for articles in any language from database inception to May 2017 using search terms developed with a reference librarian (Supporting Information Appendix S1), and scanned references sections of included articles and relevant review articles to identify additional studies. Studies of non-rifamycin antibiotics are reported separately.[10]

### Study selection and data extraction

One author (K.B.S.) performed the database search and screened titles and abstracts for initial exclusion based on study type, exposures and outcomes. Two authors independently

reviewed the full text of all articles not excluded during abstract review to determine which met the criteria for inclusion. Differences were resolved by discussion with a third author. Articles were translated into English as needed.

One author independently extracted relevant study information into evidence tables and a second author independently reviewed tables for accuracy prior to study grading (Supporting Information Appendix S2). Information recorded for each article in standardised abstraction tables included study design, objectives, population, drug exposures (contraceptive and rifamycin drugs including duration of use, dose, timing and measures of adherence), outcomes including PK parameters and criteria for detecting ovulation, primary findings for each outcome, and assessment of confounders. For PK outcomes, we recorded AUC, Cmax, Cmin, and/or mean 24-hour drug levels of contraceptive and/or rifamycin drugs alone and in combination, including the results of statistical comparisons. For clinical outcomes we recorded any reported pregnancies, frequency of ovulation based on serum progesterone with or without ultrasound, adverse health effects including frequency of irregular bleeding, and TB disease outcomes. We did not contact authors to obtain additional non-published information.

### Assessment of risk of bias in individual studies

We used the United States Preventative Services Task Force (USPSTF) grading scale (good, fair, poor) to evaluate the quality of evidence each study provided for its primary outcome. For cohort and case-control studies, we graded each of the following criteria: definition and assessment of exposures, definition and identification of outcomes, selection of controls, blinding, confounders, sample size, response rate/follow up, and internal validity.[11] As no standardised grading scale exists to assess the quality of PK studies, we utilised a rating system previously reported to evaluate studies with PK outcomes, which included assessment of study design, sample size, exposures, outcomes, timing, intersubject variability, population, steady state of perpetrator drug, and validation of assays.[12] We graded studies based on their primary outcome, but also report secondary outcomes. A study received the overall grade of good if every graded component received a score of good, and poor if one or more grading criteria was graded as poor (considered a fatal flaw that would invalidate results). All other studies were graded as fair. The quality of each study was assigned independently by two authors, and any differences were resolved through discussion with a third author.

### Data synthesis

We used evidence tables to synthesise data and quality evaluations. Findings are reported descriptively for each drug. We could not perform meta-analysis due to heterogeneity of exposures and outcomes, as well as limited data for certain drugs.

## Results

We identified unique 7361 articles in our search (Figure 1). After review of titles and abstracts, we reviewed 220 full-text articles. Eleven articles met the inclusion criteria for this review. All addressed COCs and none evaluated non-oral formulations of HC. We did not

identify any studies using pregnancy rates as an outcome. Nine studies evaluated the effect of rifamycins on HC PK or ovulation,[13–21] one evaluated the effect of HC on rifamycin PK,[22] and one evaluated the effect of HC on TB treatment outcomes.[23]

## Rifampin and rifabutin

**Surrogate measures of contraceptive effectiveness—**Four studies reported on presumed ovulation with concurrent use of rifampin and/or rifabutin with COCs, with mixed findings (Tables 1 and 2). Meyer et al.[19] performed an open label single-sequence crossover study of 22 healthy ovulating women taking levonorgestrel-containing COCs (LNG COC) with and without rifampin 300 mg daily. Based on a single ultrasound showing follicular growth and a single serum progesterone on cycle day 21, no women ovulated with COCs alone, but 50% ovulated during the rifampin/COC cycle. Joshi et al. measured serum progesterone twice between cycle days 19 and 23 in women with TB taking rifampin 8–10 mg/kg daily and norethindrone-containing COCs (NET COC), and in a group of healthy controls taking COCs. They found elevations consistent with ovulation in two of seven women with TB receiving COCs and rifampin, compared with zero of 10 in controls. In contrast, LeBel et al.[14] reported no difference in daily serum progesterone levels in 28 healthy women on days 17–19 between control cycles (NET COC alone) and cycles with rifampin 300 mg daily given on cycle days 1–10,[14] and Barditch-Crovo et al.[13] reported no elevations in a single day 21 serum progesterone measurement in 12 healthy women during NET COC cycles with rifampin 600 mg daily or rifabutin 300 mg daily taken on cycle days 8–21.[13]

**PK outcomes—**Three studies addressed COC hormone PK with rifampin, and all demonstrated reductions in estrogen and/or progestin exposure.[15–18] A single-sequence crossover study of eight women on chronic rifampin therapy for tuberculosis reported ethinyl estradiol (EE) and NET PK after a single COC pill during and after rifampin therapy.[15,16] EE and NET areas under the curve (AUC) were each approximately 42% lower, and half-lives ($t_{1/2}$) about 50% shorter when co-admi-nistered with rifampin (all $P < 0.01$). A single-sequence crossover study of nine women with tuberculosis reported COC PK parameters in the cycles before and after initiating rifampin 8–10 mg/kg daily for 23 days.[18] Mean 24 hour NET level and AUC decreased 65% and 30%, respectively, after starting rifampin (both $P < 0.05$), but EE AUC and mean 24-hour levels did not significantly change.

More recently, Blode et al.[17] reported PK of oral estradiol and dienogest (DNG) in a single-sequence crossover study of post-menopausal women taking estradiol valerate-based COCs with and without rifampin (600 mg for 5 days, $n = 6$).[17] Both estradiol and DNG levels were significantly reduced by rifampin; the geometric mean ratios (GMR) of estradiol Cmax and $AUC_{24}$ were 75% (66.9–84.4%) and 56% (53–59%), respectively, and DNG Cmax and $AUC_{24}$ GMR were 48% (44.8–51.6%) and 17% (15.6–18.7%).

Two additional studies examined both rifampin and rifabutin.[13,14] A single-sequence, four-period crossover study of 12 healthy women taking COCs reported EE and NET PK before and on the last day of a 14-day course of rifampin (600 mg daily) or rifabutin (300 mg daily).[13] With rifampin, EE $AUC_{24}$ decreased by a mean of 66% and Cmax by 43% (both $P$

< 0.01), NET $AUC_{24}$ had a mean decrease of 51% ($P < 0.001$) and Cmax was unchanged. When co-administered with rifabutin, EE $AUC_{24}$ decreased by a mean of 35% ($P < 0.001$) and Cmax was unchanged, NET $AUC_{24}$ decreased a mean of 13% ($P < 0.01$) and there was no change to Cmax. Rifampin resulted in larger changes to EE and NET parameters than rifabutin ($P < 0.05$ for all).

A single-sequence open-label crossover study reported COC PK in 28 healthy COC users before and during co-treatment with rifabutin or rifampin (both 300 mg daily for 10 days).[14] Co-therapy with rifampin decreased EE $AUC_{24}$ and Cmax by 64 and 42%, respectively, and NET $AUC_{24}$ by 60%, and rifabutin reduced EE $AUC_{24}$, EE Cmax and NET $AUC_{24}$ by 35, 20, and 46%, respectively (all differences < 0.001). Differences in EE but not NET parameters were significantly larger for rifampin than for rifabutin ($P < 0.05$).

Finally, one study reported rifampin PK in six healthy women following a single dose of rifampin during cycles with and without concurrent COCs.[22] Rifampin AUC and Cmax were unchanged between the two cycles ($P > 0.05$).

**Safety: TB disease progression and adverse events—**One prospective cohort study evaluated tuberculosis outcomes and COC-tolerability in 51 women taking rifampinor non-rifampin-based anti-TB regimens.[23] Compared with historical controls, no difference was evident in the clinical course of TB when various COCs were added to rifampin-based therapies. Although the non-rifampin group reported no menstrual irregularities on COCs, 16 of the 38 women on rifampin and COCs reported irregular spotting or bleeding.

### Rifaximin

One study addressed COC PK with rifaximin, a drug approved by the US FDA for the treatment of travelers' diarrhoea (Table 2). A single-sequence crossover study of 28 healthy women reported COC PK following a single COC pill, and again following a second single COC pill after 3 days of rifaximin (200 mg every 8 hours).[20] This study reported no difference in EE or norgestimate (NGM) AUC or Cmax GMRs before or after co-therapy.

### Rifalazil

One study addressed COC PK with the experimental drug rifalazil (Table 2). This single-sequence crossover study administered a COC to 14 postmenopausal women for 14 days, and measured EE PK before and after a single oral dose of rifalazil (25 mg) on day 8.[21] EE AUC and Cmax remained within the pre-specified GMR range of bioequivalence (CI of 80–125%) following rifalazil.

## Discussion

### Main findings

Women with medical conditions that expose them to increased health risks in pregnancy, such as TB, may be particularly motivated to avoid an unintended pregnancy.[7] The most relevant drug interaction outcomes are pregnancy (reflecting decreased contraceptive effectiveness) or TB disease progression (reflecting decreased anti-TB therapeutic

effectiveness). Although our review of rifamycin antimicrobials and HC demonstrated some evidence of drug interactions when COCs are administered with rifampin, no studies directly evaluated the risk of pregnancy. Our review also noted varying degrees of drug interaction among other rifamycins. We found no studies directly evaluating rifamycins with other HC methods and very limited data on the effect of COCs on anti-TB therapy PK or disease progression.

Surrogate markers of contraceptive effectiveness in this review showed mixed effects. In two fair quality studies, up to 50% of subjects taking rifampin with COCs had presumed ovulation diagnosed by serum progesterone (combined with a single ultrasound in one study), whereas no women ovulated on COCs alone.[18,19] Two additional good quality studies found no evidence of ovulation by serum progesterone with the COC/rifampin combination.[13,14] Breakthrough bleeding with COCs (which does not indicate ovulation but may affect pill tolerance or compliance) was more common during rifampin administration than without in two of three studies addressing this outcome (fair to poor quality).[14,23,24]

Differences in drug exposure were more consistent. Progestin exposure as measured by AUC was reduced 30–83% in five studies of good to fair quality when COCs were co-administered with rifampin compared with COCs alone.[13–15,17,18] Statistically significant reductions in progestin half-life and $C_{max}$, and increases in drug clearance, were also observed in some of these studies.[13,15,17] EE exposure by AUC was reduced by 42–66% in four of these studies when COCs were administered with rifampin compared with alone,[13,14,16,17] with similar changes noted in other PK parameters. Minimum efficacy thresholds are not defined for EE or progestins, so it is not possible to predict the degree of contraceptive compromise based on PK changes alone.[25] However, progestin levels are critical for contraception, so these significant decreases combined with the observed alterations in ovulation suppression are concerning for a possible reduction in contraceptive effectiveness when adherence-dependent methods such as COCs are combined with rifampin.

Studies of other rifamycins demonstrated less consistent effects on ovulation and contraceptive PK. Rifabutin induces and is metabolised by CYP3A4, though its degree of enzyme induction is less than rifampin.[8] No ovulation was detected by serum progesterone when COCs were combined with rifabutin, and observed PK changes were generally smaller with rifabutin than with rifampin in two studies of good quality.[13,14] Nevertheless, PK interaction was still present and a reduction in contraceptive effect remains possible with rifabutin.

No studies addressed surrogate markers of contraceptive effectiveness for rifaximin or rifalazil. In one fair quality study, rifaximin did not alter systemic progestin or EE exposure, as would be expected, as this drug is not orally absorbed and does not circulate systemically.[20] One poor quality study indicated no change to EE parameters when COCs were administered with rifalazil. Rifalazil was developed partially because it is not an inducer of CYP P450 enzymes and therefore was expected to have fewer drug interactions than rifampin. However, it was never brought into clinical use due to its side effect profile.[8] We did not identify any studies that addressed the remaining FDA-approved rifamycin,

rifapentine, with HC. This drug has an intermediate level of CYP 3A4 induction compared with rifampin and rifabutin, so a similar degree of interaction would be expected.[8]

Combined HCs also have the ability to affect metabolism of co-administered drugs, as EE is a known moderate inhibitor of several CYP P450 enzymes.[6] One poor quality study did not observe significant changes in rifampin PK when administered with COCs,[26] and another poor quality study observed no difference in TB treatment response among COC users and non-users.[23]

## Strengths and limitations

This systematic review has several strengths, including strict inclusion criteria requiring that all studies have a comparison group. COCs have a typical-use 1 year failure rate of 5–9%,[27,28] so it is inappropriate to conclude that COC failures in women using rifamycins are always due to drug interaction, as was proposed in older case series and uncontrolled observational studies.[5] Likewise, due to our inclusion of multiple pertinent outcomes, we were able to evaluate consistency of findings between PK and clinical outcomes.

However, this review is limited by the quantity and quality of published evidence. Importantly, no studies measured the most pertinent outcome of pregnancy during concurrent COC/rifamycin use, so our conclusions are based on surrogate outcomes for pregnancy risk. Policy-makers and clinicians need to consider this important limitation. Studies that addressed ovulation are limited by small sample sizes, and in some cases infrequent or poorly timed measurements of serum progesterone, which may have led to inadequate detection of ovulation. Serum progesterone is a surrogate marker for ovulation, and no studies used daily ultrasound to confirm ovulation.[19] PK studies had weaknesses including not randomising, not addressing drug adherence, small sample sizes, use of statistical comparisons that do not take into account therapeutic bioequivalence, and lack of attention to potential confounders such as body mass index. No studies addressed the combination of rifamycins with non-oral contraceptive formulations such as the transdermal patch, vaginal ring, injectables or progestin implants. Finally, data on newer rifamycins were limited to single PK studies, limiting the ability to extrapolate these findings clinically.

## Interpretation

The WHO and US Medical Eligibility Criteria for Contraceptive Use consider the use of rifampin and rifabutin with oral, patch, and ring contraceptives to be category 3, meaning that theoretical or proven risks generally outweigh advantages, due to a presumed reduction in contraceptive effect.[7,29] However, the relative risk of pregnancy in HC users taking rifamycins compared with those not taking rifamycins is unknown. Women should be informed of the theoretical risk of drug interactions but should not be denied use of any method given this important knowledge gap. In the absence of data, recommendations for injectable and implantable contraceptive methods with rifamycins are category 1 and 2, respectively, meaning safe or generally safe to use, with the caveat that contraceptive effect may be reduced with contraceptive implants. The effectiveness of progestin-only injectables appears to be unaffected by enzyme-inducting medications, due to the higher systemic exposure to progestin.[30] Given the large number of women on rifamycin therapy worldwide,

many of whom are of reproductive age, further research on interactions between rifamycins and injectable/implantable contraception is urgently needed. Intrauterine contraception does not rely on systemic drug levels and is also category 1 (safe) for women with non-pelvic TB.[7,29]

## Conclusions

Published studies of PK and ovulation outcomes support a clinically concerning drug interaction between COCs and rifampin or rifabutin, but no published studies have addressed pregnancy rates. Published data are absent for other contraceptives methods and rifapentine, and studies of rifaximin and rifalazil and COCs are limited in quality but less concerning for drug interactions. Very limited data do not demonstrate an effect of COCs on rifampin PK or TB disease outcomes. Women taking COCs with rifampin should be advised of possible drug interactions affecting contraceptive effectiveness, but should not be denied use of this method.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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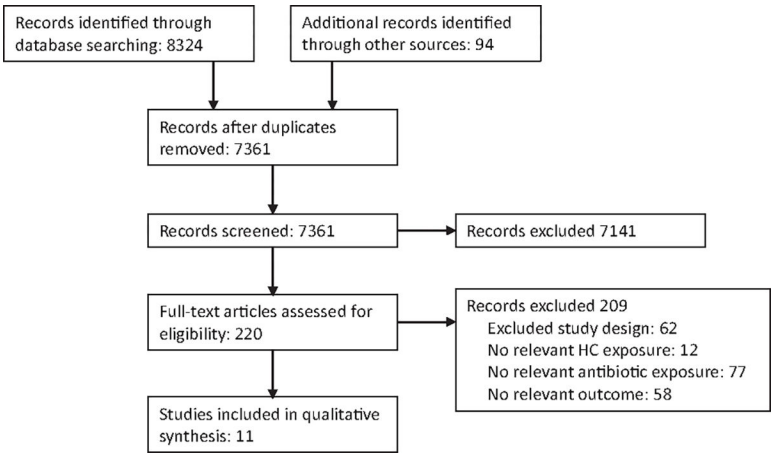


**Figure 1.**
PRISMA flow diagram.

**Table 1.**

Summary of rifampin evidence

| Author (year) | Study design | Interventions | Population | Outcomes | Interaction* | Quality |
|---|---|---|---|---|---|---|
| Bardich-Crovo (1999)[13] | Single sequence crossover | NET/EE<br>Rifampin | Healthy women: *n* = 12 | NET PK<br>EE PK<br>Serum P | NET PK: ↓↓↓<br>EE PK: ↓↓↓<br>No rise in P | Good |
| Lebel (1998)[14] | Single sequence crossover | NET/EE<br>Rifampin | Healthy women: *n* = 28 | NET PK<br>EE PK<br>Serum P<br>BTB | NET PK: ↓↓↓<br>EE PK: ↓↓↓<br>No rise in P<br>BTB: 36% rifampin subjects vs. 4% control | Good |
| Back (1979, 1980)[15,16] | Single sequence crossover | NET/EE<br>Rifampin | Women with TB: *n* = 8 | NET PK<br>EE PK | NET PK: ↓↓<br>EE PK: ↓↓ | Fair |
| Blode (2012)[17] | Single sequence crossover | E2V/DNG<br>Rifampin | Healthy post-menopausal women: *n* = 28 | E2V PK<br>DNG PK | E2V PK: ↓↓↓<br>DNG PK: ↓ | Fair |
| Joshi (1980)[18] | Single sequence crossover | NET/EE<br>Rifampin | Women with TB: *n* = 9 | NET PK<br>EE PK<br>Serum P | NET PK: ↓↓<br>EE PK: ↔<br>Serum P: 2 of 9 with elevated P | Fair |
| Meyer (1990)[19] | Single sequence crossover | LNG/EE<br>Rifampin | Healthy women: *n* = 22 | Serum P / ultrasound BTB | Ovulation by serum P/US: 0 COC alone, 50% COC/ rifampin<br>BTB: No difference | Fair |
| Gupta (1988)[22] | Single sequence crossover | NET/EE<br>Rifampin | Healthy women: *n* = 6 | Rifampin PK | Rifampin PK: ↔ | Poor |
| Reimers (1971)[23] | Prospective cohort | Various COCs<br>Rifampin | Women with TB: *n* = 51<br>Rifampin: *n* = 38<br>Nonrifampin treatment: *n* = 13 | BTB<br>TB disease course | BTB: 42% rifampin users versus 0% non-users<br>No difference in TB disease course compared with historical controls | Poor |

BTB, breakthrough bleeding; COC, combined oral contraceptive; DNG, dienogest; E2V, estradiol valerate; EE, ethinyl estradiol; LNG, levonorgestrel; NET, norethindrone; NGM, norgestimate; PK, pharmacokinetics; P, serum progesterone; TB, tuberculosis.

*Interaction reflects the outcome with the combination of COC and rifamycin compared with the outcome drug alone. Magnitude and direction of interaction represents area under the curve (AUC) when available, steady state level when not.

↔ no statistical change;

↓ statistically significant decrease of 0–25% from baseline;

↓↓ statistically statistical decrease of 26–50% from baseline;

↓↓↓ statistically significant decrease of >50% from baseline.

**Table 2.**

Summary of evidence for other rifamycins

| Author (year) | Study design | Interventions | Population | Outcomes | Interaction* | Quality |
|---|---|---|---|---|---|---|
| **Rifabutin** | | | | | | |
| Bardich-Crovo (1999)[13] | Single sequence crossover | NET/EE<br>Rifabutin | Healthy women: *n* = 12 | NET PK<br>EE PK<br>Serum P | NET PK: ↓<br>EE PK: ↓↓<br>No rise in P | Good |
| Lebel (1998)[14] | Single sequence crossover | NET/EE<br>Rifabutin | Healthy women: *n* = 28 | NET PK<br>EE PK<br>Serum P | NET PK: ↓↓<br>EE PK: ↓↓<br>No rise in P | Good |
| **Rifaximin** | | | | | | |
| Trapnell (2007)[20] | Single sequence crossover | NGM/EE<br>Rifaximin | Healthy women: *n* = 28 | EE PK<br>NGM PK | EE PK: ↔<br>NGM PK: ↔ | Fair |
| **Rifalazil** | | | | | | |
| Chen (2007)[21] | Single sequence crossover | NET/EE<br>Rifalazil | Heathy post-menopausal women: *n* = 14 | EE PK | EE PK: ↔ | Poor |

EE, ethinyl estradiol; NET, norethindrone; NGM, norgestimate; PK, pharmacokinetics; P, serum progesterone.

*Interaction reflects the outcome with the combination of COC and rifamycin compared with the outcome drug alone. Magnitude and direction of interaction represents area under the curve (AUC) when available, steady state level when not.

↔ no statistical change;

↓ statistically significant decrease of 0–25% from baseline;

↓↓ statistically statistical decrease of 26–50% from baseline;

↓↓↓ statistically significant decrease of >50% from baseline.