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

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OBJECTIVE: The purpose of this study was to determine whether interactions between non-rifamycin antibiotics and hormonal contraceptives result in decreased effectiveness or increased toxicity of either therapy.

STUDY DESIGN: We searched MEDLINE, Embase, clinicaltrials.gov, and Cochrane libraries from database inception through June 2016. We included trials, cohort, case-control, and pharmacokinetic studies in any language that addressed pregnancy rates, pharmacodynamics, or pharmacokinetic outcomes when any hormonal contraceptive and non-rifamycin antibiotic were administered together vs apart. Of 7291 original records that were identified, 29 met criteria for inclusion.

STUDY APPRAISAL AND SYNTHESIS METHODS: Two authors independently assessed study quality and risk of bias using the United States Preventive Services Task Force evidence grading system. Findings were tabulated by drug class.

RESULTS: Study quality ranged from good to poor and addressed only oral contraceptive pills, emergency contraception pills, and the combined vaginal ring. Two studies demonstrated no difference in pregnancy rates in women who used oral contraceptives with and without non-rifamycin antibiotics. No differences in ovulation suppression or breakthrough bleeding were observed in any study that combined hormonal contraceptives with any antibiotic. No significant decreases in any progestin pharmacokinetic parameter occurred during co-administration with any antibiotic. Ethinyl estradiol area under the curve decreased when administered with dirithromycin, but no other drug.

CONCLUSION: Evidence from clinical and pharmacokinetic outcomes studies does not support the existence of drug interactions between hormonal contraception and non-rifamycin antibiotics. Data are limited by low quantity and quality for some drug classes. Most women can expect no reduction in hormonal contraceptive effect with the concurrent use of non-rifamycin antibiotics.

Key words: antibiotics, contraceptive failure, drug interaction, hormonal contraception, pharmacokinetics

Millions of women worldwide rely on hormonal contraception (HC) to plan and space pregnancies and to prevent unintended pregnancies.[1] To maximize the reliability of these methods, it is important to understand whether drug interactions could contribute to HC failure or pose safety concerns. Antibiotics commonly are used by reproductive-aged women. Drug interactions between HC and antibiotics, such as induction or inhibition of hepatic enzymes by either drug, theoretically could compromise contraceptive or antibiotic effect.[2] However, clinical concerns of drug interactions between antibiotics and HC are based primarily on case reports of unintended pregnancies in HC users and patient and provider surveys that are limited severely by recall bias.[2] Likewise, although rifamycin antibiotics (rifampin, rifabutin) induce hepatic enzymes that are required for HC metabolism, other antibiotics do not; assumption of similar behavior of all antibiotic drugs may be inappropriate.[3]

Misconceptions regarding HC and drug interactions are common among women, providers, and pharmacists; a majority of pharmacists recommend backup contraception for women who use antibiotics with HC.[4] Such warnings could result in interruption of a woman's HC or poor compliance with antibiotic regimens, which could increase her risk for treatment failure with either drug. If no true drug interaction is present, these risks are assumed unnecessarily.

Objectives

The purpose of this systematic review was to evaluate published literature on the interaction of non-rifamycin antibiotics and HC. Specifically, we addressed the following research question: Among women taking HC or non-rifamycin antibiotics, do users who take these drugs together experience decreased contraceptive or antibiotic effectiveness or increased hormonal or antibiotic toxicity compared with users who take each drug alone?

Methods

This systematic review was conducted according to an a priori protocol with similar methods to previous World

TABLE 1
Summary of evidence from observational studies

Study	Study design	Data source	Exposures	Size	Outcomes	Interaction	Quality
Helms et al[11]	Retrospective cohort	3 Dermatology practices	Any OC ± any concurrent antibiotic use	356 Exposed; 425 unexposed	Pregnancy rates in antibiotic exposed vs unexposed OC users	↔	II-2, Fair
Jick et al[12]	Nested case control	United Kingdom database of general practitioners	Any OC or patch ± any antibiotic use within 16 weeks of conception	1129 Cases; 4374 controls	Odds of unintended pregnancy while on OCs in antibiotic users vs nonusers	↔	II-2, Poor
Koopmans et al[14]	Case cross-over	Pharmacy dispensing database in the Netherlands	Any OC use; any antibiotic script within 15 days of conception	397 Cases; self-matched controls	Odds of antibiotic exposure during conception vs control time periods in OC failure pregnancies	↔	II-2, Poor
Toh et al[13]	Case cross-over	Sloane Epidemiology Center Birth Defects Study and National Birth Defects Prevention Study	Any OC use during month of conception; any antibiotic use in 4 weeks before conception	1330 Cases; self-matched controls	Odds of antibiotic exposure during conception vs control time periods in OC failure pregnancies	↔	II-2, Fair

↔, no difference in the outcome between cases and controls; *OC*, oral contraceptive pill.

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Health Organization and Centers for Disease Control systematic reviews for contraceptive guidance[5,6] (protocol available on request). We report this systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[7]

Eligibility criteria, information sources, and search strategy

Types of studies. We included randomized and nonrandomized controlled trials, cohort studies, and case-control studies. Abstracts, case reports and series, cross-sectional studies, editorials, letters, and nonpublished results were excluded. All included studies were required to have a comparison group; therefore, we also excluded prospective observational studies without control groups. For studies with HC-related outcomes, the comparison group was women taking HC without concurrent antibiotics. For studies of antibiotic-related outcomes, the comparison group was women taking the antibiotic without HC.

Participants and interventions. We included studies of women taking any method of HC (combined pills, patch, ring or injectables; progestin-only pills; ring, injectables, implants or intrauterine-devices, or emergency contraceptive pills) in combination with any oral, intravenous, or intramuscular non-rifamycin antibiotic. We excluded studies of steroid hormones in non-contraceptive formulations, such as intravenous estrogen.

Types of outcomes and data items. We included studies that had at least 1 clinical or pharmacokinetic outcome of interest. Clinical outcomes of interest included (1) pregnancy rates, (2) evidence of ovulation by luteal phase serum progesterone alone or in combination with a dominant follicle on ultrasound imaging, (3) antibiotic effectiveness (treatment response or failure), and (4) adverse health effects (breakthrough bleeding, drug side-effects, or complications). Pharmacokinetic

outcomes of interest included area under the curve (AUC), maximum serum concentration (Cmax), and steady-state levels of the contraceptive steroid hormone or the antibiotic. We excluded studies that reported only urinary excretion of hormones because these were not considered interpretable pharmacokinetic findings.

Search strategy. We searched MEDLINE, Embase, Clinicaltrials.gov, and Cochrane libraries from inception to June 2016 for articles in any language using search terms that were developed with a reference librarian (Appendix A). We scanned reference lists of relevant review articles to identify additional studies that were not captured by our search.

Study selection

One author (K.B.S.) performed the database search in consultation with a reference librarian and screened all titles and abstracts. Two authors

reviewed the full text of all possible articles to determine which articles met inclusion criteria. Non-English articles were translated as needed. Any disagreement between authors on inclusion status was resolved with a third author.

Data extraction
One author independently extracted relevant information from each study to complete prespecified evidence tables. Tables were reviewed for accuracy by a second author before study grading (Appendices B—G). We included only published findings and did not contact authors to obtain additional information.

Assessment of risk of bias
We assigned a quality rating for each study that was based on the overall evidence it provided for its primary outcome, according to the United States Preventative Services Task Force grading scale (good, fair, poor).[8] A "good" study has no important limitations, and results are considered internally valid; a "fair" study has clear limitations but no fatal flaws, and a "poor" study has ≥ 1 fatal flaws that may invalidate results. In determining the study quality rating, we assessed risk of bias using prespecified grading criteria. For case-control, cohort studies and nonrandomized trials with only clinical outcomes, grading criteria for risk of bias included selection bias, appropriateness and generalizability of participants, sample size and power, exposure assessment, timing of antimicrobial use, validation of outcomes, loss to follow up, and confounding. For trials with pharmacokinetic outcomes, we used a previously reported quality rating system to assess study design, sample size, drug exposure and adherence, appropriateness of pharmacokinetic parameters, timing of blood draws, intersubject variability, steady state of perpetrator drug, and validation of assays.[9] The quality of each study was assigned independently by 2 authors. Any differences were resolved through discussion with a third author.

Data synthesis
We synthesized findings descriptively. Observational studies of pregnancy rates with general antibiotic use were described first, followed by a summary of findings for each class of antibiotic. Metaanalysis could not be conducted because of heterogeneity of exposures (different antibiotic drugs, doses, and progestins) and outcomes (differences in pharmacokinetic parameters and timing) and limited studies in most drug classes.

Results
We identified 7291 articles and 70 studies on clinicaltrials.gov in our initial search after removal of duplicates (Figure). After review of titles and abstracts, 220 full-text articles were reviewed. Twenty-nine articles met inclusion criteria, including 1 article in German.[10] No studies on clinicaltrials.gov met inclusion criteria that were not already captured by other databases. We first report observational studies of pregnancy rates or HC failure with any antibiotic use (n=4) and then report trials of individual antibiotics with clinical or pharmacokinetic outcomes (n=25).

Pregnancy rates and antibiotic use (Table 1; Appendix B)
Two studies compared pregnancy rates in women who used HC alone or with an antibiotic.[11,12] In a retrospective cohort study of 3 dermatology practices, Helms et al[11] surveyed by mail 578 women with a history of concurrent exposure to oral contraceptive pills (OCs) and antibiotics over 5 years. Of 356 women who completed the survey, 263 women also had unexposed time periods with OC use alone; investigators surveyed an additional 162 OC users without a record of concurrent antibiotic use to complete the control group. Five pregnancies occurred among women who were exposed to HCs and antibiotics (minocycline, 3; cephalosporin, 2); 12 pregnancies occurred in women who were exposed to OCs alone. There was no difference in pregnancy rates for women who used OCs alone and women who used OCs concurrently

with antibiotics (0.96 and 1.6 per 100 women-years, respectively; P=.4).

Jick et al[12] performed a nested case control study to examine risk factors for unintended pregnancy within a database of general practitioners in the United Kingdom. Cases were women with unintended pregnancy or pregnancy termination who had a prescription for HC within 4 months before the index date (date of diagnosis of unintended pregnancy; n=1129). Four women per case who used HC without a documented unintended pregnancy served as control subjects, matched by age, practice, and year. Antibiotic exposure was determined by prescription for an antibiotic within 16 weeks before the index date. The odds of unintended pregnancy were similar, regardless of antibiotic use (odds ratio [OR], 1.0; 95% confidence interval [CI], 0.8—1.2).

Two studies examined the odds of antibiotic use at the time of OC failure.[13,14] Toh et al[13] used a national birth defects database to evaluate antibiotic use in 1330 OC failure pregnancies in a case crossover study. Women served as their own controls, with risk factors for OC failure compared between the time frame of 0—4 weeks before conception (case period) to 4—8 weeks before conception (control period). The rate of antibiotic use was 4% during the case period and 3.8% during the control period (self-matched OR, 1.08; 95% CI, 0.63—1.84). Odds of antibiotic exposure were also similar with the use of an alternate control period (8—12 weeks before conception) or restricting to only ampicillin/amoxicillin use.

Finally, Koopmans et al[14] performed a case crossover study using an outpatient pharmacy dispensing database in The Netherlands. The population included women who presumably became pregnant while taking OCs (based on picking up an OC refill within the first 3 months of a pregnancy; n=397). The exposure window for any concurrent antibiotic prescription was 15 days before and after probable conception; the control windows were 1-month periods that occurred 2 months (period 1) or 1 year (period 2) before the exposure window. Odds of antibiotic use were no higher in

the exposure window than in control windows (control period 1: OR, 2.0; 95% CI, 0.89−4.79; control period 2: OR, 1.42; 95% CI, 0.64−3.25).

Penicillins/cephalosporins and OCs (Table 2; Appendix C)
Surrogate measures of contraceptive effectiveness and adverse health effects. Three small trials evaluated luteal progesterone levels in women taking OCs with and without ampicillin; none of the trials showed evidence of ovulation in cycles with concurrent ampicillin, and 1 ovulation occurred in a control cycle.[15-17] One observational study reported that 2 of 20 women with previously normal cycles on OCs experienced breakthrough bleeding after the addition of ampicillin 500 mg 4 times daily.[10]

Pharmacokinetic outcomes. Three small trials found no difference in HC pharmacokinetic when administered with ampicillin.[16-18] A single sequence crossover study of 6 healthy women examined ethinyl estradiol (EE) and norethindrone pharmacokinetic during OC alone and with ampicillin 500 mg twice daily for 5−7 days later in the same cycle.[17] EE and norethindrone AUC and mean plasma levels were unchanged after the addition of ampicillin. Likewise, a mixed parallel group and single sequence crossover study enrolled 11 postmenopausal women and administered 3 days of ampicillin (500 mg 4 times day) on days 5−8 of OCs.[18] Although no statistics were given, EE/norethindrone steady-state plasma values that were presented in graphic form did not decrease from baseline after ampicillin was added and were similar to controls. Back et al[16] conducted 2 small single sequence crossover studies of EE/levonorgestrel pharmacokinetic in 13 women taking OCs alone and with ampicillin (500 mg 3 times daily for 8 days during cycle 1 or 2). EE and levonorgestrel mean plasma concentrations were no different during cycles with and without ampicillin.

Two studies addressed pharmacokinetic outcomes for penicillins.[19,20] Philipson[19] reported plasma ampicillin levels and AUC in 10 women after a single 500-mg dose on day 21 of an OC

FIGURE
Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram
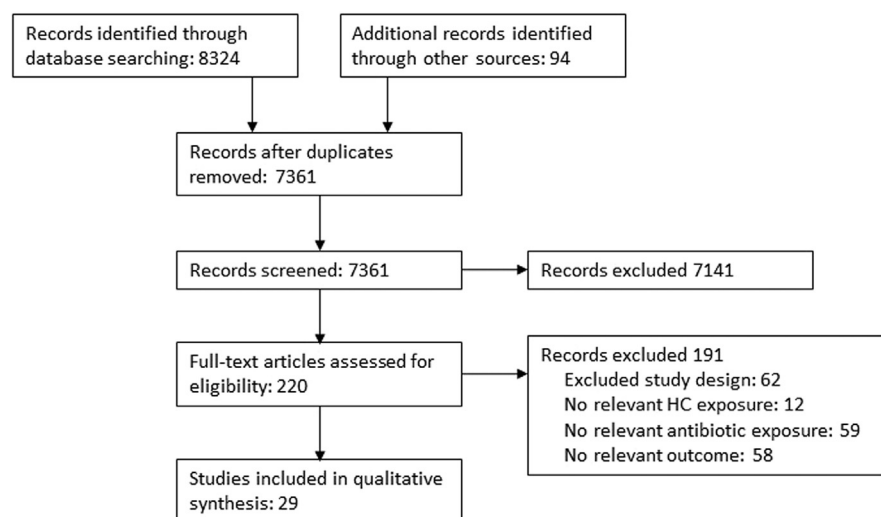
Number of articles identified in initial database search and excluded at each step of the assessment process.

HC, hormonal contraception.

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cycle and again on day 28, after a 7-day OC washout. Mean ampicillin plasma levels were lower 1 hour after dosing when administered with the OC compared with without (values not provided; $P<.05$), but at all other time points were unchanged; the total AUC and Cmax were no different. Authors concluded that the difference in ampicillin levels did not appear to be clinically important. Finally, a study of 4 women taking OCs reported cephaloridine levels over 8 hours after a 500-mg intramuscular dose on days 21 (with OC) and 28 (after washout).[20] Peak serum levels of cephaloridine were higher on day 28 than on day 21 (23.5 vs 18.9 μg/mL, no statistics given). The clinical significance of this difference was not described.

Tetracyclines and OCs (Table 2; Appendix D)
Three studies demonstrated no difference in surrogate contraceptive effectiveness or pharmacokinetic outcomes with tetracyclines.[10,21,22] Murphy et al[21] performed a mixed parallel group and single-sequence crossover study of 11 women to evaluate tetracycline and OC pharmacokinetic when administered

separately and together. EE AUC and Cmax were unchanged before and after tetracycline (500 mg every 4 hours for 10 days); norethindrone AUC_{24} and Cmax rose after tetracycline was added (AUC, 33.0−57.9 [units not provided]; Cmax, 4.5−6.3 ng/mL; $P<.01$ for both). Tetracycline AUC_{0-4} did not differ with and without OCs. Similarly, Neely et al[22] performed a single sequence crossover study of 24 women taking OCs for 2 cycles, with doxycycline 100 mg twice daily on days 14−21 during cycle 2. Norethindrone and EE steady-state levels on days 18−20 were unchanged during the control and doxycycline cycles. Days 18−20 serum progesterone concentrations were unchanged and consistent with anovulation in both cycles. For adverse health effects, a third study reported that 15 women with previously normal cycles on OCs reported no breakthrough bleeding after taking oxtetracycline (500 mg 4 times daily).[10]

Fluoroquinolones and OCs (Table 2; Appendix E)
Surrogate measures of contraceptive effectiveness and adverse health effects. Two trials reported no ovulation by luteal

TABLE 2
Summary of evidence from trials with pharmacodynamics or pharmacokinetic outcomes

Study	Study design	Interventions	Size, n	Outcomes	Interaction[a]	Quality
Penicillins						
Adlercreutz et al[18]	Single sequence crossover within parallel groups	NET/EE Ampicillin	11	NET PK EE PK	NET PK: ↔ EE PK: ↔	Poor
Back et al[16]	Single sequence crossover	LNG/EE Ampicillin	13	LNG PK EE PK Serum P	LNG PK: ↔ EE PK: ↔ No rise in P	Poor
Friedman et al[15]	Single sequence crossover	Ethynodiol acetate/EE Ampicillin	11	Serum P	No rise in P	Poor
Hempel et al[10]	Single sequence crossover	NET/EE Ampicillin	20	Bleeding changes	0/20 Control vs 2/20 with BTB	Poor
Joshi et al[17]	Single sequence crossover	NET/EE Ampicillin	6	NET PK EE PK Serum P	NET PK: ↔ EE PK: ↔ No rise in P	Fair
Philipson[19]	Single sequence crossover	LNG/EE Ampicillin	10	Ampicillin PK	Ampicillin mean level ↓ at first hour, otherwise ↔	Fair
Wise and Reeves[20]	Single sequence crossover	OC Cephaloridine intramuscular	4	Cephaloridine PK	Cephaloridine ↓	Poor
Tetracyclines						
Hempel et al[10]	Single sequence crossover	NET/EE Oxtetracycline	15	Bleeding changes	0/15 Control vs 0/15 with BTB	Poor
Murphy et al[21]	Single sequence crossover within parallel groups	NET/EE Tetracycline	11	NET PK EE PK Tetracycline PK	NET: ↑ EE: ↔ Tetracycline: ↔	Poor
Neely et al[22]	Single sequence crossover	NET/EE Doxycycline	24	NET PK EE PK Serum P	NET PK: ↔ EE PK: ↔ No rise in P	Fair
Fluoroquinolones						
Amsden et al[28]	Parallel groups	OCs/DMPA Trovafloxacin	20	Trovafloxacin PK	Trovafloxacin ↓	Poor
Back et al[27]	Single sequence crossover	LNG/EE Temafloxacin	12	LNG PK EE PK Serum P	LNG PK: ↔ EE PK: ↔ No rise in P	Fair
Csemiczky et al[26]	Randomized crossover	LNG/EE Ofloxacin	20	Serum P Ultrasound	No ovulation	Good
Droppert et al[23]	Randomized crossover	DSG/EE Ciprofloxacin	24	Serum P Ultrasound	No ovulation	Poor
Maggiolo et al[25]	Randomized crossover	EE/various progestins Ciprofloxacin	10	Bleeding changes	0/10 Control vs 0/10 with BTB	Poor
Scholten et al[24]	Randomized crossover	DSG/EE Ciprofloxacin	24	EE PK Serum P	EE PK: ↔ No rise in P	Good
Shain et al[29]	Parallel groups	OC Moxifloxacin	30	Moxifloxacin PK	Moxifloxacin ↓	Fair
Macrolides						
Back et al[31]	Single sequence crossover	LNG or DSG/EE Clarithromycin	10	LNG PK EE PK Serum P	LNG PK: ↔ EE PK: ↔ No rise in P	Fair

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TABLE 2
Summary of evidence from trials with pharmacodynamics or pharmacokinetic outcomes (continued)

Study	Study design	Interventions	Size, n	Outcomes	Interaction[a]	Quality
Blode et al[33]	Single sequence crossover	E2V/DNG Erythromycin	12	E2V PK DNG PK	E2V ↑ DNG ↑	Fair
Fischer et al[34]	Parallel groups	OCs Azithromycin	25	Azithromycin PK	Azithromycin ↑	Poor
Meyer et al[30]	Single sequence crossover	LNG/EE Roxithromycin	22	Serum P Ultrasound	No ovulation	Fair
Wermeling et al[32]	Single sequence crossover	NET/EE Dirithromycin	15	EE PK Serum P	EE ↓ No rise in P	Good
Others antibiotics						
Hempel et al[10]	Single sequence crossover	NET/EE Trimethoprim/ sulfamethoxazole	21	Bleeding changes	0/21 Control vs 2/21 with BTB	Poor
Hempel et al[10]	Single sequence crossover	NET/EE Nitrofurantoin	18	Bleeding changes	0/18 Control vs 0/18 with BTB	Poor
Joshi et al[35]	Parallel groups	NET/EE Dapsone	16	NET PK EE PK	NET PK: ↔ EE PK: ↑	Fair
Joshi et al[17]	Single sequence crossover	NET/EE Metronidazole	25	NET PK EE PK Serum P	NET PK: ↔ EE PK: ↔ No difference in P	Fair
Mehrota et al[36]	Parallel groups	Mestranol/EE Isoniazid/ streptomycin	83	TB outcomes	No difference in TB outcomes	Poor
Other contraceptive formulations						
Dogterom et al[38]	Randomized crossover	ENG/EE CVR Amoxicillin	16	ENG PK EE PK	ENG PK: ↔ EE PK: ↔	Good
Dogterom et al[38]	Randomized crossover	ENG/EE CVR Doxycycline	16	ENG EE PK	ENG PK: ↔ EE PK: ↔	Good
Pohl et al[37]	Single sequence crossover	UPA Erythromycin	18	UPA PK	UPA ↑	Good

[a] Interaction reflects the outcome with the combination of HC and antibiotic, compared with the outcome drug alone. Direction of interaction represents summary of PK changes to reflect overall exposure. ↓, statistically significant decrease in drug exposure; ↔, no change in drug exposure; ↑, statistically significant increase in drug exposure; *BTB*, breakthrough bleeding; *CVR*, contraceptive vaginal ring; *DMPA*, depo-medroxyprogesterone acetate; *DNG*, dienogest; *DSG*, desogestrel; *E2V*, estradiol valerate; *EE*, ethinyl estradiol; *ENG*, etonogestrel; *LNG*, levonorgestrel; *NET*, norethindrone; *OC*, oral contraceptive pill; *P*, progesterone; *PK*, pharmacokinetics; *TB*, tuberculosis; *UPA*, ulipristal acetate.

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progesterone and no difference in ovarian activity by ultrasound scanning in OC cycles with and without ciprofloxacin.[23,24] One trial reported no breakthrough bleeding in OC cycles with and without ciprofloxacin.[25] Two additional trials reported no ovulation by serum progesterone and/or monitoring of follicles on ultrasound scanning in OC cycles with and without temafloxacin or ofloxacin.[26,27]

Pharmacokinetic outcomes. Two studies reported no change to HC pharmacokinetic with fluoroquinolones.[24,27] In a single sequence crossover study of 12

women using OCs over 2 cycles, with a 7-day course of temafloxacin 600 mg daily starting in cycle 2, steady-state plasma levels of EE and levonorgestrel on days 5—8 were no different in the temafloxacin cycle than with OCs alone.[27] Likewise, a double-blind, randomized controlled crossover study of 24 women using OCs with ciprofloxacin 500 mg twice daily or placebo for the first 10 days of 2 cycles found no difference in EE AUC_{24} or Cmax geometric mean ratios (GMRs) between cycles.[24]

Two studies reported small, but clinically unclear, reductions in

fluoroquinolone pharmacokinetic with OCs.[28,29] One parallel group study reported trovafloxacin pharmacokinetic after a single 200-mg dose in women using HC (OCs or depot medroxyprogesterone acetate) or non-HC.[28] Trovafloxacin Cmax and AUC were lower in the HC group (Cmax, 2.27 vs 1.92 mg/L; AUC, 26.7 vs 20.8 mg/L), and clearance was higher (7.62 vs 9.96 L/h; all comparisons $P<.004$). A second parallel group study reported moxifloxacin pharmacokinetic after a single 400-mg dose for women using OCs or non-HC.[29] They observed no difference in Cmax between groups, but AUC_{0-48} was

15% lower (P=.008), and clearance was 20% higher (P=.015) in the OC group. The clinical significance of these changes was not addressed in either study.

Macrolides and OCs (Table 2; Appendix F)

Surrogate measures of contraceptive effectiveness and adverse health effects. Three trials reported no ovulation by ultrasound scanning and/or luteal progesterone during OC cycles with and without roxithromycin, clarithromycin, or dirithromycin.[30-32] There was also no difference in breakthrough bleeding between cycles with and without roxithromycin or dirithromycin.[30,32]

Pharmacokinetic outcomes. Three studies reported mixed HC pharmacokinetic outcomes with macrolides.[31-33] Back et al[31] performed a single-sequence crossover study of 10 OC users and measured OC steady-state plasma levels during cycles with and without clarithromycin 250 mg twice daily on days 1−7. Day 5−8 EE and levonorgestrel plasma steady-state levels were unchanged between the 2 cycles (P>.1), and 3-ketodesogestrel (the primary metabolite of desogestrel) increased slightly with clarithromycin (3.35 vs 1.43 ng/mL; P<.02). Wermeling et al[32] reported day-8 EE pharmacokinetic in a single sequence crossover study of 15 women using OCs alone and with dirithromycin 500 mg daily during days 21−28 of cycle 2 and days 1−8 of cycle 3. They found a small, but significant, decrease in mean EE AUC (7.6%; P=.03) and an increase in EE clearance (10%; P=.03) in the dirithromycin cycle, but no change in Cmax. Blode et al[33] reported pharmacokinetic of estradiol and dienogest in a single sequence crossover study of postmenopausal women taking estradiol valerate (E2V)/dienogest with and without erythromycin (500 mg 3 times daily for 5 days; n=12). Contraceptive exposure increased when E2V/dienogest was administered with erythromycin; estradiol Cmax and AUC$_{24}$ GMRs were 151% (95% CI, 136−168%) and 133% (95% CI, 118−150%), respectively; dienogest Cmax and AUC$_{24}$ GMRs were 133% (95% CI, 123−144%)

and 162% (95% CI, 146−180%), respectively.

A single paper reported azithromycin pharmacokinetic in 2 small parallel group studies of women using OCs (n=10) or not (n=15), taking 500 mg oral azithromycin followed by 250 mg daily for 4 days.[34] The AUC of azithromycin was higher for OC users than for nonusers (mean difference, 11.4 mg-h/L; 95% CI, 5.7-17.2 mg-h//L), and azithromycin clearance was 38% lower in OC users. Clinical implications were not evaluated.

Other antibiotics and OCs (Table 2; Appendix G)

One single sequence crossover study of 10 women examined metronidazole (400 mg 3 times daily for cycle days 7−14) in combination with OCs.[17] Compared with a cycle with OCs alone, day 14 EE and norethindrone steady state, Cmax, and AUC$_{24}$ were not significantly different. In a group of 25 women (the original 10 plus an additional 15 women taking the same drug combination), luteal progesterone was consistent with ovulation for 3 of 25 metronidazole cycles and 2 of 25 control cycles.

Joshi et al[35] reported OC pharmacokinetic for OCs administered with dapsone (100 mg 5 days per week) in 10 women with leprosy compared with OCs alone in 6 control women. Norethindrone Cmax and AUC$_{24}$ were similar in both groups; EE AUC$_{0-8}$ was higher in dapsone patients than control patients (1041 vs 682 pg/mL/hr; P<.05), and EE Cmax was not significantly different.

In a single sequence crossover study, Hempel et al[10] reported bleeding patterns before and after the addition of sulfamethoxazole/trimethoprim (3 times daily) or nitrofurantoin (100 mg 4 times daily) to OCs. Compared with a history of no disordered bleeding with OCs alone, 2 of 22 women taking sulfamethoxazole/trimethoprim reported disordered bleeding while on the antibiotic, and none of 18 women on nitrofurantoin reported disordered bleeding.

Finally, Mehrota et al[36] followed tuberculosis disease outcomes in women

using isoniazid-based antibiotic regimens with and without OCs over 1 year. Sputum cultures were negative for all 33 women who received OCs and for 32 of 34 non-OC patients at the end of the year.

Other contraceptive formulations (Table 2; Appendix G)

Pohl et al[37] reported ulipristal acetate (UPA) pharmacokinetic in a single sequence crossover study of 18 healthy women with and without erythromycin (500 mg twice daily for 9 days). UPA Cmax and AUC$_{24}$ GMRs increased in the presence of erythromycin (24% [95% CI, 1−52%] and 224%, [95% CI, 175-283%], respectively); the primary UPA metabolite showed an increase in AUC$_{24}$ of 62% (43−85%) and a decrease in Cmax by 48% (95% CI, 38−56%). UPA was well tolerated with and without erythromycin, and no serious adverse events occurred.

Dogterom et al[38] performed 2 randomized crossover studies of the EE/etonogestrel contraceptive vaginal ring (CVR) with and without amoxicillin (875 mg twice daily days 1−10; n=16) or with and without doxycycline (100 mg daily days 1−10; n=16) over 2 cycles. With the use of the data in the GMRs and 90% CIs, there was no difference in EE or etonogestrel AUC$_{12}$ with amoxicillin or AUC$_{24}$ with doxycycline compared with control cycles.

Comment
Main findings

Unintended pregnancy is a great concern for women taking HC with potentially interacting drugs. In this systematic review, 2 studies of fair-to poor quality found no increased risk of pregnancy in OC users taking antibiotics (any type), compared with OC users not taking antibiotics.[11,12] Two additional fair-to-poor quality studies found no higher odds of antibiotic use at the time of conception in OC-breakthrough pregnancies than in control time periods.[13,14] Although additional older studies that were excluded from this review reported contraceptive failure in OC users taking antibiotics or reported antibiotic use among women with pill failures, none of

those studies had comparison groups, which makes it impossible to draw conclusions on the role of the antibiotic in those pregnancies.[2]

Surrogate markers of contraceptive effectiveness in this review also support no interaction between the use of non-rifamycin antibiotics and HC. Although most ovulation outcomes were secondary and often underpowered (Appendices C–G), no differences in ovulation by serum progesterone or ultrasound scanning were observed in any study that combined OCs with ampicillin,[15-17] doxycycline,[22] temafloxacin,[27] ofloxacin,[26] ciprofloxacin,[23,24] clarithromycin,[31] roxithromycin,[30] dirithromycin,[32] or metronidazole.[17] Likewise, breakthrough bleeding was either no different than control or inconclusive in combination with ampicillin,[10] oxtetracycline,[10] ciprofloxacin,[25] dirithromycin,[32] roxithromycin,[30] nitrofurantoin,[10] or trimethoprim/sulfamethoxazole.[10]

Finally, pharmacokinetic outcomes were also reassuring for no interaction between HC and non-rifampicin antibiotics. Importantly, no significant decreases in any progestin or EE parameter occurred during co-administration with antibiotics that included ampicillin or amoxicillin (4 good-to-poor quality studies),[16-18,38] tetracycline or doxycycline (3 good-to-poor quality studies),[21,22,38] temafloxacin or ciprofloxacin (2 good-to-fair quality studies),[24,27] clarithromycin or erythromycin (2 fair-quality studies),[31,33] or dapsone or metronidazole (1 fair-quality study each; Table 2).[17,35] UPA geometric mean peak levels and AUC increased during co-administration with erythromycin in 1 good quality study.[37] Although there is a wide range in quality and design of these studies, the consistency of results is reassuring that progestin levels, which are critical to contraceptive effect, are not reduced when co-administered with non-rifamycin antibiotics.

The only statistically significant decrease in any EE parameter occurred during co-administration with dirithromycin (a drug no longer available in the United States). EE AUC decreased

7.6%, but Cmax was unchanged in 1 good-quality study.[32] Decreases in systemically active EE may result in the development of a dominant follicle because of insufficient suppression of folliculogenesis, but ovulation suppression should still be maintained by suppression of luteinizing hormone by the progestin component.[39] An increase in some EE and E2V pharmacokinetic parameters occurred with co-administration with dapsone and erythromycin, respectively.[33,35] Increases in estrogen exposure theoretically could affect thrombosis risk, although this outcome was not addressed in any study.

Combined HCs can also affect metabolism of co-administered antibiotics, potentially altering safety or effectiveness profiles. EE is a known moderate inhibitor of several cytochrome P450 (CYP) enzymes and could increase concentrations of drugs that are metabolized by these enzymes.[3] Two poor-quality studies of cephaloridine and azithromycin reported statistical increases in antibiotic pharmacokinetic parameters during co-administration with OCs, which has uncertain clinical significance but could pose theoretic drug toxicity concerns.[20,34] Although EE is not a known inducer of CYP enzymes (which would reduce levels of co-administered drugs), 2 fair-to-poor quality studies reported statistical reductions in some trovafloxacin and moxifloxacin pharmacokinetic parameters when taken with OCs, which could pose theoretic treatment concerns if reductions were large enough to affect the therapeutic range.[28,29] No change to ampicillin and tetracycline pharmacokinetic parameters was seen in 2 fair-to-poor quality studies with OCs.[19,21] None of these studies reported toxicity or antibiotic treatment failure outcomes in conjunction with pharmacokinetic outcomes, limiting their interpretation and utility.

Strengths and limitations
This systematic review has several strengths. Primarily, we used strict inclusion criteria that required that all studies include a comparison group. This is important because combined

HCs have a typical-use failure rate of 9%,[40] so it is inappropriate to assume that combined HC failures in women who use antibiotics are due to drug interaction, as was theorized in older uncontrolled observational studies, case series, and guidelines that were based on case reports.[2,41] Likewise, our inclusion of a range of clinical and pharmacokinetic outcomes allows for evaluation of consistency of findings and better extrapolation to clinical care.

However, this review is limited by the quality and quantity of published evidence. The observational studies faced degrees of misclassification bias of antibiotic and HC exposures and pregnancy outcomes (Appendix B). They are also limited by grouping antibiotics (which may dilute smaller effects), an inability to assess contraceptive adherence, and a lack of adjustment for confounders. Studies that addressed ovulation faced limitations that included small sample sizes and infrequent or poorly timed measurements of progesterone, which may have led to missed ovulations in some cases (Appendices C–G). Few studies used ultrasound scanning to monitor follicular development and rupture; serum progesterone is itself a surrogate marker for ovulation. Pharmacokinetic studies had various weaknesses that included not assessing adherence to 1 or both drugs, small sample sizes, use of non-standardized pharmacokinetic parameters, the use of statistical comparisons that do not take into account therapeutic bioequivalence, a lack of randomization, and a lack of attention to potential confounders (Appendices C–G). It is also difficult to draw clinical conclusions from pharmacokinetic studies alone because minimum efficacy thresholds are not established for EE or progestins.[42] Finally, only 1 study examined a non-OC formulation (CVR).[38] No data exist on the combination of antibiotics with other non-oral formulations that include the transdermal patch, injectables, or progestin implants. Studies of OCs included a range of doses and progestins, but none included the lowest dose pills (ie, containing <30 μg EE or <150 μg

levonorgestrel). We did not attempt to normalize findings based on EE or progestin dosing. Therefore, the findings of this review may not extrapolate to the lowest dose pills that contain 10–25 μg EE or <150 μg levonorgestrel.

Theoretic mechanisms for contraceptive failure with antibiotics include alterations in drug absorption or metabolism. Decreases in intestinal bacteria, which transform orally ingested EE before absorption and enterohepatic circulation by the small intestine, could reduce absorption of contraceptive steroids.[43] However, enterohepatic circulation contributes relatively little to circulating EE and progestin levels for most women, so its reduction is unlikely to have a significant effect on systemic levels.[43,44] Metabolism may be altered by induction or inhibition of hepatic enzymes. Rifampin is the only antibiotic known to induce CYP enzymes, which could increase the rate of EE and progestin metabolism and potentially compromise contraceptive effect.[3] Although some antibiotics are known inhibitors of CYP enzymes (ciprofloxacin, clarithromycin, erythromycin, metronidazole, trimethoprim, and telethromycin),[3] this interaction would increase steroid levels, which would not compromise contraceptive mechanisms but theoretically could increase side-effects. Studies of UPA and E2V/dienogest reported increases in steroid hormones when co-administered with erythromycin, but side-effects did not increase for UPA and were not reported for E2V/dienogest.[33,37] Finally, antibiotics could reduce biologically active progestin levels through increased production of sex hormone binding globulin, which is an hepatic protein that binds progestins. Although rifampin induces the production of sex hormone binding globulin, other antibiotics do not.[2]

Despite the reassuring evidence presented in this review, there are individual variations in CYP metabolism that are based on genetics and ethnicity, and there may be a small subset of women (likely <1%) who are more susceptible to HC failure at baseline because of these factors.[44,45] Likewise, enterohepatic circulation is altered in obesity, and it is unknown whether obese women are more susceptible to drug interactions as a result. Contraceptive failure on a particular method, particularly when compliance has been good, may suggest a higher risk of repeat failure on that method, and such women should consider switching to a more effective method or adding backup contraception.

Comparison with existing literature

Our findings are consistent with current contraceptive guidance from the 2016 United States Medical Eligibility Criteria for Contraceptive Use[6] and the 2015 World Health Organization Medical Eligibility Criteria for Contraceptive Use,[5] which recommend no restriction for the use of any method of HC with broad spectrum antibiotics. Likewise, the most recent guidance for dental practitioners[46] and from the American Academy of Dermatology Association[47] no longer advise use of additional contraceptive protection during use of non-rifamycin antibiotics.

Conclusions and implications

Existing evidence does not support drug interactions between HC and non-rifamycin antibiotics. Data are limited by insufficient quantity and quality for some antibiotic drug classes (particularly metronidazole, sulfa drugs, and nitrofurantoin) and non-OC formulations. Most women can expect no reduction in HC effect with concurrent use of non-rifamycin antibiotics. To maximize the effectiveness of user-dependent methods like OCs, providers should encourage correct and consistent use at all times, including during illness. ∎

REFERENCES

1. Trends in contraceptive use worldwide. In: Department of Economic and Social Affairs PD, ed. New York: United Nations; 2015.

2. Dickinson BD, Altman RD, Nielsen NH, Sterling ML; Council on Scientific Affairs AMA. Drug interactions between oral contraceptives and antibiotics. Obstet Gynecol 2001;98:853-60.

3. Guidance for industry: Drug interaction studies - study design, data analysis, implications for dosing, and labeling recommendations. In: Food and Drug Administration, ed. 2012. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf. Accessed June 7, 2017.

4. Masters KP, Carr BM. Survey of pharmacists and physicians on drug interactions between combined oral contraceptives and broad-spectrum antibiotics. Pharm Pract (Granada) 2009;7:139-44.

5. Medical Eligibility Criteria for Contraceptive Use: World Health Organization, 2015. Available at: http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/. Accessed May 18, 2017.

6. United States medical eligibility criteria for contraceptive use, 2016. MMWR Morb Mortal Wkly Rep 65;3:1-103.

7. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

8. US Preventative Services Task Force. Grade definitions. 2016. Available at: https://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions#grade-definitions-after-may-2007. Accessed June 7, 2017.

9. Berry-Bibee EN, Kim MJ, Simmons KB, et al. Drug interactions between hormonal contraceptives and psychotropic drugs: a systematic review. Contraception 2016;94:650-67.

10. Hempel E, Zorn C, Graf K. Effect of chemotherapy agents and antibiotics on hormonal contraception [German]. Z Arztl Fortbild 1978;72:924-6.

11. Helms SE, Bredle DL, Zajic J, Jarjoura D, Brodell RT, Krishnarao I. Oral contraceptive failure rates and oral antibiotics. J Am Acad Dermatol 1997;36:705-10.

12. Jick SS, Hagberg KW, Kaye JA, Jick H. The risk of unintended pregnancies in users of the contraceptive patch compared to users of oral contraceptives in the UK General practice research database. Contraception 2009;80:142-51.

13. Toh S, Mitchell AA, Anderka M, de Jong-van den Berg LT, Hernandez-Diaz S; National Birth Defects Prevention S. Antibiotics and oral contraceptive failure: a case-crossover study. Contraception 2011;83:418-25.

14. Koopmans PC, Bos JH, de Jong van den Berg LT. Are antibiotics related to oral combination contraceptive failures in the Netherlands? A case-crossover study. Pharmacoepidemiol Drug Saf 2012;21:865-71.

15. Friedman CI, Huneke AL, Kim MH, Powell J. The effect of ampicillin on oral contraceptive effectiveness. Obstet Gynecol 1980;55:33-7.

16. Back DJ, Breckenridge AM, MacIver M, et al. The effects of ampicillin on oral contraceptive steroids in women. Br J Clin Pharmacol 1982;14:43-8.

17. Joshi JV, Joshi UM, Sankholi GM, et al. A study of interaction of low-dose combination oral contraceptive with ampicillin and metronidazole. Contraception 1980;22:643-52.

18. Adlercreutz H, Pulkkinen MO, Hamalainen EK, Korpela JT. Studies on the role of intestinal bacteria in metabolism of synthetic and natural steroid hormones. J Steroid Biochem 1984;20:217-29.

19. Philipson A. Plasma and urine levels produced by an oral dose of ampicillin 0.5 G administered to women taking oral contraceptives. Acta Obstet Gynecol Scand 1979;58: 69-71.

20. Wise R, Reeves DS. Two aspects of the availability of cephalosporins after intramuscular injection. J Antimicrob Chemother 1975;1: 47-52.

21. Murphy AA, Zacur HA, Charache P, Burkman RT. The effect of tetracyclines on levels of oral contraceptives. Am J Obstet Gynecol 1991;164:28-33.

22. Neely JL, Abate M, Swinker M, D'Angio R. The effect of doxycycline on serum levels of ethinyl estradiol, norethindrone, and endogenous progesterone. Obstet Gynecol 1991;77: 416-20.

23. Droppert RA, Scholten PC, Zwinkels M, Hoepelman IM, Te Velde ER. Lack of influence of ciprofloxacin on the effectiveness of oral contraceptives. Drugs 1993;46:286-7.

24. Scholten PC, Droppert RM, Zwinkels MGJ, Moesker HL, Nauta JJP, Hoepelman IM. No interaction between ciprofloxacin and an oral contraceptive. Antimicrob Agent Chemother 1998;42:3266-8.

25. Maggiolo F, Puricelli G, Dottorini M, Caprioli S, Bianchi W, Suter F. The effect of ciprofloxacin on oral contraceptive steroid treatments. Drugs Exp Clin Res 1991;17:451-4.

26. Csemiczky G, Alvendal C, Landgren BM. Risk for ovulation in women taking a low-dose oral contraceptive (microgynon) when receiving antibacterial treatment with a fluoroquinolone (ofloxacin). Adv Contracept 1996;12:101-9.

27. Back DJ, Tjia J, Martin C, et al. The lack of interaction between temafloxacin and combined oral contraceptive steroids. Contraception 1991;43:317-23.

28. Amsden GW, Mohamed MA, Menhinick AM. Effect of hormonal contraceptives on the pharmacokinetics of trovafloxacin in women. Clin Drug Investig 2001;21:281-6.

29. Shain CS, Whitaker AM, Amsden GW. Effects of oral contraceptives on the pharmacokinetics of moxifloxacin in premenopausal women. Clin Drug Investig 2002;22: 429-34.

30. Meyer B, Muller F, Wessels P, Maree J. A model to detect interactions between roxithromycin and oral contraceptives. Clin Pharmacol Ther 1990;47:671-4.

31. Back DJ, Tjia J, Martin C, Millar E, Salmon P, Orme M. The interaction between clarithromycin and combined oral-contraceptive steroids. J Pharm Med 1991;1:81-7.

32. Wermeling DP, Chandler MH, Sides GD, Collins D, Muse KN. Dirithromycin increases ethinyl estradiol clearance without allowing ovulation. Obstet Gynecol 1995;86:78-84.

33. Blode H, Zeun S, Parke S, et al. Evaluation of the effects of rifampicin, ketoconazole and erythromycin on the steady-state pharmacokinetics of the components of a novel oral contraceptive containing estradiol valerate and dienogest in healthy postmenopausal women. Contraception 2012;86:337-44.

34. Fischer JH, Sarto GE, Habibi M, et al. Influence of body weight, ethnicity, oral contraceptives, and pregnancy on the pharmacokinetics of azithromycin in women of childbearing age. Antimicrob Agents Chemother 2012;56: 715-24.

35. Joshi JV, Maitra A, Sankolli G, Bhatki S, Joshi UM. Norethisterone and ethinyl estradiol kinetics during dapsone therapy. J Assoc Physicians India 1984;32:191-3.

36. Mehrotra ML, Gautam KD, Pande DC, et al. Compatibility of oral contraceptive with antitubercular chemotherapy in female pulmonary tuberculosis patients. Indian J Med Res 1974;62:1782-6.

37. Pohl O, Osterloh I, Gotteland JP. Effects of erythromycin at steady-state concentrations on the pharmacokinetics of ulipristal acetate. J Clin Pharm Ther 2013;38:512-7.

38. Dogterom P, Van Den Heuvel MW, Thomsen T. Absence of pharmacokinetic interactions of the combined contraceptive vaginal ring NuvaRing with oral amoxicillin or doxycycline in two randomized trials. Clin Pharmacokinet 2005;44:429-38.

39. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility, 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.

40. Trussell J. Contraceptive failure in the United States. Contraception 2011;83:397-404.

41. American Dental Association Council on Scientific Affairs. Antibiotic interference with oral contraceptives. J Am Dent Assoc 2002;133:880.

42. Cherala GE, Edelman AB, Dorflinger L, Stanczyk FZ. The elusive minimum threshold concentration of levonorgestrel for contraceptive efficacy. Contraception 2016;94:104-8.

43. Edelman AC, Cherala GE, Stanczyk FZ. Metabolism and pharmacokinetics of contraceptive steroids in obese women: a review. Contraception 2010;82:314-23.

44. Weisberg E. Interactions between oral contraceptives and antifungals/antibacterials. Is contraceptive failure the result? Clin Pharmacokinet 1999;36:309-13.

45. Goldzieher JS, Stanczyk FZ. Oral contraceptives and individual variability of circulating levels of ethinyl estradiol and progestins. Contraception 2008;78:4-9.

46. Taylor J, Pemberton MN. Antibiotics and oral contraceptives: new considerations for dental practice. Br Dent J 2012;212:481-3.

47. Hormonal agents: Recommendations: American Academy of Dermatology Association. Available at: https://www.aad.org/practicecenter/quality/clinical-guidelines/acne/hormonal-agents. Accessed June 13, 2017.

Appendix A Search strategy

MEDLINE: (Contraceptive Agents, Female/ OR exp Contraceptives, Oral/ OR exp Intrauterine Devices, Medicated/) OR ((Levonorgestrel/ OR Ethinyl Estradiol-Norgestrel Combination/ OR exp Progesterone/ OR exp Progestins/) and (contracept* OR birth control).ti,ab,kf,hw.) OR ((progest* OR Levonorgestrel OR ethinylestradiol OR estradiol OR Norgestrel OR etonogestrel OR oral OR pill OR tablet OR hormon* OR steroid OR inject* OR depo* OR medroxyprogesterone OR dmpa OR net-en OR norethisterone enanthate OR patch* OR transdermal OR implant* OR long acting OR intravaginal OR intra-vaginal OR ring* OR post coital OR postcoital) AND (contracept* OR birth control)).ti,ab,kf,hw. OR (norplant* OR (intrauterine ADJ2 device*) OR (intra-uterine ADJ2 device*) OR (intrauterine ADJ2 contracept*) OR (intrauterine ADJ2 system*) OR (intra-uterine ADJ2 contracept*) OR (intra-uterine ADJ2 system*) OR LNG-IUS OR IUD? OR IUS OR IUCD? OR ((intra-vaginal OR intra-vaginal OR vaginal) ADJ2 ring*)).ti,ab,kf,hw.

AND

Exp anti-infective agents/ or exp anti-bacterial agents/ or exp antifungal agents/ or exp anti-infective agents, local/ or exp antiparasitic agents/ or antiviral agents/ OR (Anti-infective OR anti-microbial OR antimicrobial OR antiinfective OR antibiotic* OR microbicide* OR antiviral* OR anti-viral* OR anti-fungal* OR antifungal* OR fungicide* OR antimalarial* OR anti-malarial* OR antiparasitic* OR anti-parasitic* OR antibacterial* OR anti-bacterial* OR bacteriocid* OR antimycobacterial* OR anti-mycobacterial* OR antiparasitic* OR anti-parasitic* OR parasiticide*).ti,ab,kf,hw.

EMBASE: (Contraceptive Agent/ OR exp oral contraceptive agent/ OR exp intrauterine contraceptive device/ OR injectable contraceptive agent/ or postcoitus contraceptive agent/) OR ((Levonorgestrel/ OR Ethinyl Estradiol-Norgestrel Combination/ OR exp Progesterone/ OR exp Progestins/) and (contracept* OR birth control).ti,ab.) OR ((progest* OR Levonorgestrel OR ethinylestradiol OR estradiol OR Norgestrel OR etonogestrel OR oral OR pill OR tablet OR hormon* OR steroid OR inject* OR depo* OR medroxyprogesterone OR dmpa OR net-en OR norethisterone enanthate OR patch* OR transdermal OR implant* OR long acting OR intravaginal OR intra-vaginal OR ring* OR post coital OR postcoital) AND (contracept* OR birth control)).ti,ab. OR (norplant* OR (intrauterine ADJ2 device*) OR (intra-uterine ADJ2 device*) OR (intrauterine ADJ2 contracept*) OR (intrauterine ADJ2 system*) OR (intra-uterine ADJ2 contracept*) OR (intra-uterine ADJ2 system*) OR LNG-IUS OR IUD? OR IUS OR IUCD? OR ((intravaginal OR intra-vaginal OR vaginal) ADJ2 ring*)).ti,ab.

AND

antiinfective agent/ OR exp quinoline derived antiinfective agent/ OR anti-bacterial agents/ OR antifungal agents/ OR antiparasitic agent/ OR antibiotic agent/ OR (Anti-infective OR anti-microbial OR antimicrobial OR antiinfective OR antibiotic* OR microbicide* OR antiviral* OR anti-viral* OR anti-fungal* OR antifungal* OR fungicide* OR antimalarial* OR anti-malarial* OR antiparasitic* OR anti-parasitic* OR antibacterial* OR anti-bacterial* OR bacteriocid* OR antimycobacterial* OR anti-mycobacterial* OR antiparasitic* OR anti-parasitic* OR parasiticide*).ti,ab.

Cochrane: ([mh "Contraceptive Agents, Female"] OR [mh "Contraceptives, Oral"] OR [mh "Intrauterine Devices, Medicated"]) OR (([mh Levonorgestrel] OR [mh "Ethinyl Estradiol-Norgestrel Combination"] OR [mh Progesterone] OR [mh Progestins]) and (contracept* OR birth control):ti,ab) OR ((progest* OR Levonorgestrel OR ethinylestradiol OR estradiol OR Norgestrel OR etonogestrel OR oral OR pill OR tablet OR hormon* OR steroid OR inject* OR depo* OR medroxyprogesterone OR dmpa OR net-en OR norethisterone enanthate OR patch* OR transdermal OR implant* OR long acting OR intravaginal OR intra-vaginal OR ring OR post coital OR postcoital) AND (contracept* OR birth control)):ti,ab OR ((intrauterine NEAR/2 device*) OR (intra-uterine NEAR/2 device*) OR (intrauterine NEAR/2 contracept*) OR (intrauterine NEAR/2 system*) OR (intra-uterine NEAR/2 contracept*) OR (intra-uterine NEAR/2 system*) OR LNG-IUS OR IUD? OR IUS OR IUCD? OR ((extrauterine OR extra uterine) NEAR/2 coil*) OR ((intravaginal OR intra-vaginal OR vaginal) NEAR/2 ring*)):ti,ab

AND

[mh "anti-infective agents"] OR [mh "anti-bacterial agents"] OR [mh "antifungal agents"] OR [mh "antiparasitic agent"] OR [mh "anti-infective agents, local"] OR [mh "antiviral agents"] OR (Anti-infective OR anti-microbial OR antimicrobial OR antiinfective OR antibiotic* OR microbicide* OR antiviral* OR anti-viral* OR anti-fungal* OR antifungal* OR fungicide* OR antimalarial* OR anti-malarial* OR antiparasitic* OR anti-parasitic* OR antibacterial* OR anti-bacterial* OR bacteriocid OR antimycobacterial* OR anti-mycobacterial* OR antiparasitic* OR anti-parasitic* OR parasiticide*):ti,ab

Clinicaltrials.gov: "antimicrobial and contraception" "antibiotic and contraception"

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APPENDIX B
Evidence from observational studies

Study and funding	Study design	Population	Exposures	Confounders	Outcomes	Results	Strengths	Weaknesses	Quality rating
Helms et al (1997); funding not stated	Retrospective cohort	Antibiotic exposed: 578 women with concurrent antibiotic/ OC prescriptions in 3 dermatology practices over 5 years; 356 of these women completed surveys and included in analysis. Unexposed:162 women in same practices who took OCs without antibiotics, plus 263 exposed women with control periods of no antibiotic use	From medical records: OC use (any active prescription); any antibiotic use in record during OC use (confirmed concurrent use by survey)	Age, marital status, particular antibiotic and OC length of combined exposure, sexual activity during combined exposure, and use of barrier contraception; adjusted only for age	Pregnancy: Noted in medical record or reported by survey and confirmed by telephone call. Powered to detect difference of 2 pregnancies per 100 woman-years	Pregnancy rates:Antibiotics and OCs:1.6/100 woman-years. OCs alone: 0.96/100 woman years (p=.4). Five pregnancies on concurrent antibiotics (n=3 minocycline and 2= cephalosporin), some of these had missed OC doses and also had pregnancies while on OCs alone	Adjusted for age; excluded women not at risk of pregnancy or using other contraception; performed subgroup analyses for 2 control groups with same results	Control group older; antibiotics grouped together; did not adjust for pill compliance; exposure/outcome assessment limited by survey/chart review; possible misclassification if antibiotics used but not prescribed by this practice; 62% response rate	II-2; Fair
Jick et al (2009); funded by Ortho McNeil Janssen	Nested case control	Database of 300 general practitioners in United Kingdom. Cases: Unintended pregnancy in database with script for HC within 4 mo (n=1129), verified a sample of these by medical record. Control subjects: 4 Control subjects per case matched by age, practice, and year, on HC with no pregnancy (n=4374)	HC: Script in database for OC or patch. Antibiotic: Any script within 16 weeks of index pregnancy	Collected data on body mass index, smoking, duration of contraceptive use, previous abortions and deliveries, sexually transmitted infection history, alcohol/drug use, postpartum status, and use of antibiotics and anticonvulsants for case control	Pregnancy: By codes for unintended pregnancy or termination of pregnancy. Reviewed medical records to validate diagnosis and timing of exposure/outcome	Antibiotic use not associated with unintended pregnancy: OR, 1.0 (95% CI, 0.8—1.2). Adjustment for likelihood of exposure (based on timing of antibiotic use) did not change the OR	Low risk of selection bias; examined multiple potential confounders; large sample size; subgroup analyses by likelihood and timing of exposure all consistent	Did not examine antibiotics as a risk factor for pills and patch separately; did not assess compliance; attempted to validate exposure status by provider questionnaire but only surveyed 8%; up to 36% of pill user cases not exposed, and up to 59% of patch users not exposed; misclassification bias; outcome assessment may have missed pregnancies not coded as unplanned	II-2; Poor

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APPENDIX B

Evidence from observational studies *(continued)*

Study and funding	Study design	Population	Exposures	Confounders	Outcomes	Results	Strengths	Weaknesses	Quality rating
Koopmans et al (2012); funding not stated	Case cross-over study	Mothers 15—49 years old, living with their child, identified through a pharmacy dispensing database in the Netherlands. Cases: Pregnancies in OC users (n=397)	OC: OC script picked up from an outpatient pharmacy in first 3 mo of pregnancy (not first time users). Antibiotic: Any script for antibiotic during exposure window	Self-control	Odds of exposure to antibiotic during exposure/control window. EW: 15 days before and after probable conception (DOB - 270 days). CW 1: month starting 2 mo before EW; CW 2: month exactly 1 year before EW. Subgroup analysis: broad spectrum antibiotics	Breakthrough pregnancies accounted for 1.3% of total pregnancies in database. Case crossover OR: 2.00 (95% CI, 0.89—4.79) for control window 1 and OR, 1.42 (95% CI, 0.64—3.25) for control window 2. Sensitivity analysis: Broad spectrum abs: OR, 0.86 (95% CI, 0.24—2.98) for CW1 and OR, 0.71 (95% CI, 0.18—2.61) for CW2	No selection bias with self-controls; sensitivity analysis with same conclusion	Database limited to women living with their child (estimated 35% pregnancies excluded); exposure/ outcomes limited entirely to database; no external validation; proportion of breakthrough pregnancies only 1.3%, which seems low and suggests misclassification	II-2; Poor
Toh et al (2011); unfunded	Case cross-over study	Unplanned pregnancies in the Sloane Epi Center Birth Defects Study and National Birth Defects Prevention Study, both interview-based databases. Cases: 1330 Reported unplanned pregnancies while on OCs	OC: Use of OCs the month before and during conception (as recorded in database). Antibiotic: Any antibiotic use in database during reference time periods	Self-control; adjusted for transient factors like infection	Self-matched OR comparing antibiotic use for 4 wks before conception (case period) and 4—8 wks before conception (control period). Additional sensitivity analyses: (1) alternate control period, (2) stratified by antibiotic class, (3) databases separately and combined (no heterogeneity found and therefore combined)	Rate of antibiotic use was 4% during case period and 3.8% during control period. Self-matched OR, 1.08 (95% CI, 0.63 —1.84) for women who took antibiotic in only 1 of the 2 time periods. Adjusting for urinary tract infection of upper respiratory infection, OR, 1.1 (95% CI, 0.63—1.93) No diff by smoking, alcohol use body mass index. Alternate control period: OR, 1.45 (95% CI, 0.85 —2.5) for antibiotic overall and OR, 1.55 (95% CI, 0.72—3.3) for ampicillin/ amoxicillin	No selection bias with self-control; large sample size; exposure assessment obtained by structured interview; consistent findings in sensitivity analyses	Did not control for sexual activity, backup contraception; unclear generalizability; databases use primarily women with birth defects who may have recall bias about medication use	II-2; Fair

abs, antibiotics; *CW*, control window; *DOB*, date of birth; *EW*, exposure window; *HC*, hormonal contraception; *OC*, oral contraceptive pill; *OR*, odds ratio.

Simmons. Antibiotics and hormonal contraception. Am J Obstet Gynecol 2018.

APPENDIX C
Evidence for penicillins/cephalosporins

Study and funding	Study design	Population	Exposures (HC, antibiotic)	Outcomes	Results	Strengths	Weaknesses	Quality rating
Adlercreutz et al (1984); Ford foundation, Singrid Juselius Foundation, Yrjo Jahnsson Foundation, Medical Research Council of the Academy of Finland	PK; single sequence crossover/ parallel groups	11 Healthy post-menopausal women (hospital employees); ages and BMI not reported	1: 10 mg NET for 10 d (n=3), 5 mg NET for 10 d (n=1), then 10 mg NET (n=2) or 5 mg NET (n=1) for 13 d 2: 50 μg EE, 250 μg lynestrenol or 50 μg EE with 2 mg NET daily (n=4). Oral ampicillin 500 mg 4 times daily, days 5—8	1: Daily serum levels (Cmin) and day 4 and 8 PK. 2: Day 8 PK	1: No change to NET levels with NET/ ampicillin co-administration. 2: No change to EE with ampicillin co-administration (values and statistics not reported)	Perpetrator drug at steady state	Not randomized; no clear study design; small sample size; adherence not assessed; PK parameters and timing not uniform; no information on potential confounders; postmenopausal population with uncertain generalizability	Poor
Back et al (1982); supported by MRC, WHO, Mersey Health, Wellcome trust, Wyeth	PK and PD; single sequence crossover	Group 1: 7 women with UTI or URI taking OCs for at least 3 mo, ages 19—27 y, BMI not reported. Group 2: 6 healthy women taking OCs at least 3 mo, ages 21—24 y, BMI not reported	G1: OCs with 30 μg EE and 250 μg LNG (n=5); 30 μg EE and 150 μg LNG (n=1); 50 μg EE and 1 mg NET (n=1). G2: OCs with 30 μg EE and 250 μg LNG (n=5), 30 μg EE and 150 μg LNG (n=1). Ampicillin 500 mg 3 times daily for 8 days during either cycle 1 or 2	EE and progestin PK on days 5—8 cycle 1 and cycle 2. Group 2 only: ovulation by serum P days 21 and 23, break-through bleeding	G1: Ampicillin, no ampicillin; mean EE, 46.4 ± 15.2 pg/mL, 60.2 ± 14.8 pg/mL (NS); mean LNG, 2.0 ± 0.3 ng/mL, 2.05 ± 0.4 ng/mL (NS). G2: Ampicillin, no ampicillin; mean EE, 28.2 ± 2.8 pg/mL, 31.4 ± 5 pg/mL (NS); mean LNG, 2 ± 0.59 ng/mL, 2.13 ± 0.63 ng/mL (NS). No elevations in serum P, no breakthrough bleeding	Measured ampicillin level to assess adherence	Not randomized; small sample size; PK looking only at steady state 12 and 24 hr after dose; no information on potential confounders; ampicillin not detected in serum of 4 of 7 G1 patients, which raises question of validity of results	Poor
Friedman et al (1980); funded by Searle and Co	PD; single sequence crossover	11 Healthy women; ages 21—39 y, BMI not reported	OC with 50 μg EE and 1 mg ethynodiol acetate for 3 cycles. Ampicillin 250 mg or placebo 4 times daily on days 1—16 for 2 consecutive cycles	Serum P on days 13 and 19; side-effects and break-through bleeding	P levels under luteal phase levels in all cycles; 2 women had breakthrough bleeding in ampicillin cycle, 1 in the placebo cycle	Both drugs at steady state	Not randomized; small sample size; adherence not assessed; no information on potential confounders; P4 levels measured on day 19, which may have missed peak	Poor

Simmons. Antibiotics and hormonal contraception. Am J Obstet Gynecol 2018.

APPENDIX C
Evidence for penicillins/cephalosporins (continued)

Study and funding	Study design	Population	Exposures (HC, antibiotic)	Outcomes	Results	Strengths	Weaknesses	Quality rating
Hempel et al (1978); funding not stated	PD; single sequence crossover	20 Healthy women with regular menstrual cycles; age and BMI not reported	OC with 50 μg EE and 1 mg NET for at least 6 mo. Ampicillin 500 mg 4 times daily (duration not stated)	Frequency of bleeding irregularities	0/20 with disordered bleeding by historical report; 2/20 with breakthrough bleeding; 1/20 with no withdrawal bleeding after addition of ampicillin		Retrospective control period; no justification of sample size; adherence not assessed; no information on potential confounders; no information on outcome assessment	Poor
Joshi et al (1980); supported by Schering, World Health Organization	PK and PD; single sequence crossover	6 Healthy women, ages 20—36 y, BMI not reported	OC with EE 30 μg and NET 1 mg. Ampicillin 500 mg twice daily for 5—7 days starting day 6—7 of OC	EE and NET PK before start of ampicillin and again on last day of treatment; ovulation by serum P on days 19—23	EE: (before, after ampicillin) AUC_{0-6} 397 ± 46, 376 ± 71 (NS); Cmax 90 ± 11 pg/mL, 91 ± 13 pg/mL (NS). NET: (before/after ampicillin) AUC_{0-24} 125 ± 20, 128 ± 19 (NS); Cmax 11.1 ± 2.1 ng/ml, 13.7 ± 2.3 ng/ml (NS). P levels anovulatory in all cycles	PK parameters and timing appropriate, both drugs at steady state	Not randomized; small sample size; adherence data by recall only; no information on potential confounders	Fair
Philipson (1979); funding not stated	PK; single sequence crossover	10 Healthy women taking OCs; ages 20—32, weight range 50—71kg	OCs with 50 μg EE and 0.25 mg LNG (n=8), 50 μg EE and 0.5 mg LNG (n=1), 50 μg EE and 2.5 mg lynestrenol (n=1). One dose 500 mg ampicillin on day 21 and 28 of cycle	Ampicillin PK	Ampicillin mean plasma level lower at 1 hr after dose when co-administered with OC (numbers not provided; $P<.05$), no difference over remaining 8 hr or with Cmax, AUC_{0-8}, or clearance	PK parameters appropriate; some attempt to minimize intersubject variability; perpetrator drug at steady state	Not randomized; small sample size; timing of ampicillin dose to OC not addressed; adherence not assessed	Fair

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(continued)

APPENDIX C
Evidence for penicillins/cephalosporins (continued)

Study and funding	Study design	Population	Exposures (HC, antibiotic)	Outcomes	Results	Strengths	Weaknesses	Quality rating
Wise and Reeves (1975); funding not stated	PK; single sequence crossover	4 Healthy women taking OCs; ages and BMI not reported	Unspecified OC formulations; 500 mg cephaloridine IM on day 21 and again on day 28	Cephaloridine levels over 8-hr period	Cephaloridine: Cmax 18.9 μg/mL with OCs and 23.5 μg/mL without	PK parameters and timing appropriate; perpetrator drug at steady state	Not randomized; small sample size; adherence not assessed; no information on potential confounders; no information on type of OC; no statistics performed	Poor

AUC, area under the curve; *BMI*, body mass index; *Cmax*, maximum serum concentration; *Cmin*, minimum serum concentration; *EE*, ethinyl-estradiol; *HC*, hormonal contraception; *IM*, intramuscular; *LNG*, levonorgestrel; *NET*, norethindrone; *NS*, not significant; *OC*, oral contraceptive pill; *P*, progesterone; *PD*, pharmacodynamics; *PK*, pharmacokinetic; *URI*, upper respiratory infection; *UTI*, urinary tract infection.

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APPENDIX D
Evidence for tetracyclines

Study and funding	Study design	Population	Exposure (HC, antibiotic)	Outcomes	Results	Strengths	Weaknesses	Quality rating
Hempel et al (1978); funding not stated	PD; single sequence crossover	15 Healthy women with regular menstrual cycles; age and BMI not reported	OC with 50 μg EE and 1 mg NET for at least 6 mo; oxtetracycline 500 mg 4 times daily, duration not stated	Frequency of bleeding irregularities	0/15 with disordered bleeding by historical report; 0/15 with breakthrough bleeding with oxtetracycline	None	Retrospective control period; no justification of sample size; adherence not assessed; no information on potential confounders; no information on outcome assessment	Poor
Murphy et al (1991); National Institutes of Health, National Institutes of Child Health and Human Development	PK; single sequence crossover/ parallel groups	7 Healthy women (antibiotic group), 4 healthy controls; ages 18—35 y, BMI not reported	OC with 35 μg EE and 1 mg NET; tetracycline 500 mg every 4 hr for 5—10 d, starting day 2 of OC	EE and NET PK day 0 and between days 5 and 10; tetracycline AUC on day 1 and between days 5 and 10	EE: No significant changes in AUC or Cmax with tetracycline. NET: AUC and Cmax rose over time (days 0 —day) when administered with tetracycline ($P<.01$). Tetracycline: No difference in tetracycline Cmax and AUC 0-4 with OCs vs 4 control subjects (parallel analysis)	Adherence assessed with pill counts, PK parameters appropriate, perpetrator drug at steady state	Not randomized; small sample size; timing of PK measurements variable and within subject comparisons made at different times of same cycle; no information on potential confounders	Poor
Neely et al (1991); supported by West Virginia Faculty Senate and Johnson and Johnson	PK and PD; single sequence crossover	24 Women taking OCs; ages 18—35 y, BMI not reported	OC with 35 μg EE and 1 mg NET for 2 cycles; doxycycline, 100 mg twice daily days 14—21 in cycle 2	EE and NET steady-state levels on days 18-20; serum P on days 18, 19, 20 of both cycles	EE: No significant differences in serum EE with/without doxycycline ($P=.49$); NET: No significant differences in serum NET with/without doxycycline ($P=.36$). None of the women had P >0.8 ng/mL and no difference in P between cycles ($P=.32$)	Sample size reasonable, adherence assessed with pill counts, PK parameters and timing appropriate, minimized intersubject variability, perpetrator drug at steady state	Not randomized; included ovulation as an outcome, but timing of serum P not likely to be relevant, given mid-cycle administration of doxycycline	Fair

AUC, area under the curve; *BMI*, body mass index; *Cmax*, maximum serum concentration; *EE*, ethinyl-estradiol; *HC*, hormonal contraception; *NET*, norethindrone; *OC*, oral contraceptive pill; *P*, progesterone; *PD*, pharmacodynamics; *PK*, pharmacokinetic.

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APPENDIX E
Evidence for fluoroquinolones

Study and funding	Study design	Population	Exposure (HC and antibiotic)	Outcomes	Results	Strengths	Weaknesses	Quality rating
Amsden et al (2001); support by Bassett Healthcare	PK; parallel groups	Controls: 10 White women, mean age 33 ± 7.4 y, using non-HC. HC: 10 White women, mean age 31 ± 7.4 y taking HC for at least 3 mo. All normal weight	OCs (n=9); DMPA (n=1); single dose 200 mg trovafloxacin	Trovafloxacin PK over 24 hr	Both groups did not tolerate medicine in fasted state with neurologic or gastrointestinal symptoms in 80% control, 90% HC. Cmax: No HC 2.27 vs HC 1.92 mg/L (P=.03). Clearance: No HC 7.62 vs HC 9.96 L/h (P<.004). AUC: No HC 26.7 vs HC 20.8 mg/L-h (P<.004)	PK parameters and timing appropriate; limited intersubject variability	Not randomized; parallel design; small sample size; adherence not assessed; unclear whether HC at steady state because time of cycle not stated; pooled 2 hormonal methods	Poor
Back et al (1991); supported by Abbot	PK and PD; single sequence crossover	12 Healthy women on OCs at least 6 mo without breakthrough bleeding, ages 22–32 y, weight range 44–79 kg	OC with 30 μg EE+150 μg LNG (n=11); 30 μg EE and 250 μg LNG (n=1); temafloxacin 600 mg daily × 7 d start of cycle 2	EE and progestin levels on days 5–8 cycles 1 and 2; ovulation by serum P days 19–21	EE concentration 61.4 ± 21.1 pg/mL in control cycle and 68.5 ± 26.6 pg/mL in temafloxacin cycle (NS). LNG concentration 2.07 ng/mL in control cycle and 1.89 in temafloxacin cycle (NS). Plasma P concentration <1.0 ng/mL in both control and temafloxacin cycles	Adherence measured by diary card and temafloxacin levels; PK outcomes and timing appropriate; limited intersubject variability; both drugs at steady state	Not randomized; sample size marginal; data combined from multiple pill formulations	Fair
Csemiczky et al (1996); funding not stated	PD; randomized crossover (each with 2 cycles placebo and 2 cycles antibiotic)	20 Healthy women on OCs at least 3 mo, mean age 28.2 y, mean BMI 22.1 kg/m²	OC with 30 μg EE+150 μg LNG; ofloxacin 200 mg or placebo twice daily for first 7 d of each cycle	P on days 19–21 (<3 nmol/L); ultrasound 4 times per cycle for follicle >15 mm	No difference in ovarian activity between placebo and ofloxacin cycles; 3 women had follicular activity (follicle >15 mm) and high estradiol levels in both placebo and ofloxacin cycles; no women ovulated based on serum P	Randomized, double blind, adherence by diary card and tablet counts; multiple cycles of observation; timing of P measurement appropriate; exposure clear; minimal loss to follow up (n=1)	Method of randomization unclear; no mention of allocation concealment; sample size calculations not mentioned	Good

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APPENDIX E
Evidence for fluoroquinolones (continued)

Study and funding	Study design	Population	Exposure (HC and antibiotic)	Outcomes	Results	Strengths	Weaknesses	Quality rating
Droppert et al (1993), funding not stated	PD; randomized crossover	24 Healthy women, ages and weights not provided	30 μg EE, 150 desogestrel; ciprofloxacin 500 mg twice daily or placebo days 8—17 during cycle 1 and cycle 3	Ovulation by ultrasound (follicle >18 mm) and P4 at unspecified times (<2 ng/mL)	No ovulations noted by P; in 4 placebo and 4 Cipro cycles, follicles >10 mm seen —incomplete ovarian suppression; 2 placebo cycles had follicles >18 mm	Randomized, double blind	Unclear method of randomization; no mention of allocation concealment; sample size small for clinical outcome; adherence not assessed; timing of ovulation assessment not described; no description of subjects	Poor
Maggiolo et al (1991); supported by Bayer	PD; randomized crossover	10 Healthy volunteers taking long-term OCs, mean age 27.4 y; mean weight 61.4 kg, height 163.1 cm	OCs: EE 20—40 μg+gestodene 75 μg, LNG 50—150 μg, or desogestrel 150 μg (no. not stated); ciprofloxacin 500 mg or placebo twice daily for first 7 d of cycles 2 and 3	Bleeding pattern by diary	No breakthrough bleeding	Randomized; adherence monitored by pill tracking; minimized intersubject variability	Method of randomization unclear; no mention of allocation concealment	Poor
Scholten et al (1998); assistance from Organon personnel	PK and PD; randomized crossover	24 Healthy women using OCs for 3 mo; ages 19—32 y; normal weight	OC with 30 μg EE+150 μg desogestrel; ciprofloxacin 500 mg or placebo twice daily days 1—10 of cycles 1 and 3	EE PK on days 11,16; ovulation by serum P (days 16, 20, 24, 28) and ultrasound of follicles on days 8, 10, 12, 14 (follicle >18 mm)	EE PK: Geometric mean ratios for AUC$_{0-12}$, Cmax, and t$_{1/2}$ with and without Cipro were within 80—125% on days 11 and 16, considered bioequivalent; no P >2 ng/mL; 2 with sustained follicular growth (>10 mm) on placebo without ovulation	Randomized; sample size adequate; adherence measured by Cipro levels; PK parameters and timing appropriate; minimized intersubject variability; drugs at steady state	Method of randomization unclear; no mention of allocation concealment; no progestin PK; timing of progesterone measurements may have missed ovulation	Good

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APPENDIX E
Evidence for fluoroquinolones (continued)

Study and funding	Study design	Population	Exposure (HC and antibiotic)	Outcomes	Results	Strengths	Weaknesses	Quality rating
Shain et al (2002); supported by Bayer	PK; parallel groups	Control: 15 Healthy women, mean age 37.6 ± 7.2 y. HC: 15 Healthy women, mean age 31.1 ± 8.6 y using OC for at least 3 mo, normal weight	Unspecified OCs; single dose 400 mg moxifloxacin	Moxifloxacin PK over 48 hr	Moxifloxacin PK: NS difference in Cmax, Tmax, half-life with and without OC. AUC_{0-48}: OC 34.5 mg*h/L vs non-OC 40.4 mg*h/L, $P=.008$. Clearance: OC 191.3 vs non-OC 159.9 mL/min, $P=.015$; side-effects common	Sample size reasonable; PK parameters and timing appropriate; minimized intersubject variability	Not randomized; OC adherence not assessed; OC type unspecified; timing of moxifloxacin during cycle not specified; unclear whether OC at steady state	Fair

AUC, area under the curve; *BMI*, body mass index; *Cmax*, maximum serum concentration; *DMPA*, depo-medroxyprogesterone acetate; *EE*, ethinyl-estradiol; *HC*, hormonal contraception; *L-h*, liters per hour; *LNG*, levonorgestrel; *NS*, not significant; *OC*, oral contraceptive pill; *P*, progesterone; *PD*, pharmacodynamics; *PK*, pharmacokinetic; *Tmax*, time to maximum serum concentration.

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APPENDIX F
Evidence for macrolides

Study and funding	Study design	Population	Exposure (HC, antibiotic)	Outcomes	Results	Strengths	Weaknesses	Quality rating
Back et al (1991); Abbott laboratories	PK and PD; single sequence crossover	10 Healthy women taking OCs, ages 19—30 y, weight 46.3—67.4 kg	OC with 30 μg EE and 150 μg LNG (n=5) or 30 μg EE and 150 μg desogestrel (n=5), 250 mg clarithromycin twice daily days 1—7 during cycle 2	Days 5—8: 12 hr after dosing. OC: Steady state plasma EE, LNG, 3-keto desogestrel. Days 19—21: Plasma P	EE: (clarithromycin/ without) 63.3/ 59.4 pg/ mL (NS). LNG: 2.01 /1.69 ng/mL (NS). 3Ketodsg: 3.35/ 1.43 ng/mL, $P<.02$ (increased). No rise in P in either cycle	Adherence assessed with tablet counts and diaries and clarithromycin levels on days 5—7; PK parameters and timing appropriate; basic subject characteristics provided; perpetrator drug at steady state	Not randomized; small sample size	Fair
Blode et al (2012); Bayer	PK; single sequence crossover	12 Healthy postmenopausal women (confirmed by FSH, estradiol), ages 45—75 y, normal BMI	OC with estradiol valerate 2 mg/DNG 3 mg days 1—14, erythromycin 500 mg 3 times daily on days 8—14	E2V and DNG PK, antibiotic PK	E2: GMR of Cmax with/ without erythromycin: 151% (136—168%), AUC_{0-24} 133% (118 —150%). DNG: Cmax 133% (123—144%), AUC_{0-24} 162 (146 —180%). Steady state exposure up to 33% for E2 and 62% for DNG	Sample size reasonable; PK parameters and timing appropriate; minimized intersubject variability; both drugs at steady state	Not randomized; adherence not assessed; population not reproductive aged but explanation provided	Fair
Fischer et al (2012); Office of Women's Health, US Food and Drug Administration; National Institutes of Health	PK; parallel groups	25 Healthy women, 10 used OCs, ages >18 y, weight within 25% of ideal body weight	OC, unspecified types, 500 mg azithromycin day 1, 250 mg days 2—5	Azithromycin PK on day 5 and over the following 96 hours (16 samples)	Azithromycin: AUC higher when administered with OCs: (mean difference, 11.4; 95% confidence interval, 5.7—17.2 mg-h/L). Clearance 38% lower when administered with OCs	Adherence assessed by interview; diary and plasma levels; PK parameters appropriate; basic subject characteristics provided; perpetrator drug at steady state	Not randomized; small sample size; timing of azithromycin in cycle not standardized; OC type and dose unspecified	Poor
Meyer et al (1990); funding not stated	PD; single sequence crossover	22 Healthy women using either IUD or vasectomy, ages >18 y, BMI not reported	OC with EE 30/40/50 μg+LNG 50/75/125 μg during cycles 2—4, roxithromycin 150 mg twice daily during cycle 3	Ovulation by ultrasound on day 13 to show developing follicle and day 21 serum P, intermenstrual bleeding by diary	All women ovulated during baseline cycle. OC alone: 0/22 ovulated OC+roxithromycin: 0/22 ovulated. No difference in intermenstrual bleeding during 3 OC cycles	Power calculation discussed for 15% risk of ovulation; ultrasonographers were blinded to treatment; both drugs at steady state	Not randomized; bleeding outcomes may be confounded by use of IUD and triphasic pill; no information on potential confounders	Fair

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APPENDIX F
Evidence for macrolides (continued)

Study and funding	Study design	Population	Exposure (HC, antibiotic)	Outcomes	Results	Strengths	Weaknesses	Quality rating
Wermeling et al (1995); Lilly	PK and PD; single sequence crossover	15 Healthy women using OCs, ages 18—40 y, weight within 15% of ideal body weight	OC with 35 μg EE and 0.5/0.75/1 mg NET, dirithromycin 500 mg daily for 14 days (day 21 of cycle 2 through day 8 of cycle 3)	EE PK on day 8 of both cycles, ovulation by serum P on day 21 of cycle 3 and ultrasound, breakthrough bleeding	EE: AUC decreased 7.6% with dirithromycin (P=.03); clearance increased 10% (P=.03). No difference to Cmax, Tmax, half-life. No woman ovulated in either cycle. Intermenstrual bleeding: 2 women with OC alone but not with dirithromycin 1; woman with dirithromycin but not OC alone	Sample size reasonable; adherence assessed with pill diaries; PK parameters and timing appropriate; minimized intersubject variation; both drugs in steady state	Not randomized	Good

AUC, area under the curve; *BMI*, body mass index; *Cmax*, maximum serum concentration; *DNG*, dienogest; *E2*, estradiol; *E2V*, estradiol valerate; *EE*, ethinyl estradiol; *FSH*, follicle-stimulating hormone; *GMR*, geometric mean ratio; *HC*, hormonal contraception; *IUD*, intrauterine device; *LNG*, levonorgestrel; *NET*, norethindrone; *OC*, oral contraceptive pill; *P*, progesterone; *PD*, pharmacodynamics; *PK*, pharmacokinetic; *Tmax*, time to maximum serum concentration.

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APPENDIX G
Evidence for other antibiotics and non-oral formulations of hormonal contraception

Study and funding	Study design	Population	Exposure (HC and antibiotic)	Outcomes	Results	Strengths	Weaknesses	Quality rating
Hempel et al (1978); funding not stated	PD; single sequence crossover	39 Healthy women with regular menstrual cycles, age and BMI not reported	EE: 50 μg/NET unspecified. Trimethoprim/ sulfamethoxazole 3 times daily (n=21). Nitrofurantoin 100 mg 4 times daily (n=18), unspecified duration	Frequency of bleeding irregularities	Trimethoprim/ sulfamethoxazole 2/21 with disordered bleeding. Nitrofurantoin 0/18 with disordered bleeding		Retrospective control period; no justification of sample size; adherence not assessed; no information on confounders; no information on outcome assessment	Poor
Joshi et al (1984); supported by Schering	PK; parallel groups	10 Female leprosy patients on dapsone, 6 healthy controls, ages 19—38 y, normal weight	One OC (1 mg norethisterone and 30 μg EE) at 9 AM. Dapsone 100 mg 5 days per week (long-term use)	NET and EE PK	NET: Cmax Dapsone 14.6 vs 12.4 ng/mL control; AUC_{0-24} Dapsone 88.8 vs 67.1 ng/mL/hr control; all NS EE: AUC_{0-8} Dapsone 1041 vs 681 pg/m¹/hr ($P<.05$); Cmax 184 dapsone vs 128 pg/mL control (NS)	PK parameters and timing appropriate; Dapsone at steady state	Not randomized; small sample size; adherence to Dapsone not assessed; minimal attempt to minimize intersubject variation	Fair
Joshi et al (1980); supported by Schering, World Health Organization	PK and PD; single sequence crossover	10 Healthy women (PK and PD), 15 healthy women (PD only), ages 20—36 y, BMI not stated	OC with EE 30 μg+NET 1 mg. Metronidazole 400 mg 3 times daily for 6—8 days starting cycle 2 day 7	EE and NET PK (before and after completion of antibiotic); ovulation by serum P on days 19—23	EE AUC_{0-6} and NET AUC_{0-24} did not change significantly after addition of metronidazole. OCs did not alter levels of metronidazole. 3/25 Women on metronidazole/OC had ovulatory level P; 2/25 had high P during control cycle	Borderline sample size; PK parameters and timing reasonable; both drugs at steady state	Not randomized; adherence to OCs assessed, but by recall only; minimal data on intersubject variation; multiple ovulations in both groups concerning for poor adherence or assay problem	Fair
Mehrota et al (1974); funding not stated	Clinical; parallel groups	83 Female patients with pulmonary TB but otherwise healthy, with <15 d of treatment, ages 16—40 y, BMI not stated	OCs: OC with 0.1 mg mestranol and 1 mg ethynodiol diacetate. Antibiotics: 300 g isoniazid+150 mg thiacetazone daily, plus streptomycin 1g injection twice weekly for first 12 wk	TB status and safety outcomes in each group after 1 y	1 Patient died of pulmonary TB in the no OC group; 1 woman died of other causes in OC group. Sputum culture: negative for 100% of OC users at 1 year, and negative for 94% of no OC group	Randomized; groups had similar disease status at baseline by x-ray and sputum cultures	Not blinded; no information on randomization scheme; unclear power for outcomes; adherence not assessed; close to 20% LTFU in both groups	Poor

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APPENDIX G
Evidence for other antibiotics and non-oral formulations of hormonal contraception (continued)

Study and funding	Study design	Population	Exposure (HC and antibiotic)	Outcomes	Results	Strengths	Weaknesses	Quality rating
Dogterom et al (2005); funded by Organon	PK; randomized crossover	16 Healthy women per drug, ages 18–40 y, BMI 18–30 kg/m^2	Combined vaginal ring (15 μg EE+120 μg of ENG daily) for 21 days with amoxicillin 875 mg twice daily or doxycycline 100 mg daily on days 1–10 or placebo during cycles 2 and 3	EE and ENG PK	No differences in etonogestrel or EE steady-state levels or AUC between subjects using CVR with or without either antibiotic (GMRs between 0.8 and 1.25)	Randomized with details on randomization scheme; adequate SS; PK measures and timing appropriate; adherence monitored; minimized intersubject variability; both drugs at steady state	None identified	Good
Pohl et al (2013); funded by Preglem SA	PK; single sequence crossover	18 Healthy women, mean age 26.4 y (range, 19–41 y), BMI 18.5–25 kg/m^2	20 mg UPA on days 1 and 13. Erythromycin 500 mg twice daily on days 9–17	UPA PK on days 1 and 13	Cmax increased by 24% (GMR, 1.24 (90% confidence interval, 1.01–1.52); AUC$_{0-24}$ of UPA increased 3.24 (2.75–3.83; up 224%); no change to Tmax or half-life. For PGL4002 (UPA metabolite) half-life doubled, Cmax down by 48% (GMR point estimate 0.523 [95% CI 0.44–0.62]) but AUC increased by 62% (GMR point estimate 1.62 [95% CI 1.43-1.85]); no change to Tmax	Sample size adequate; standard PK parameters and timing; compliance monitored; limited intersubject variability; erythromycin at steady state	Not randomized; did not use standard EC dose	Good

AUC, area under the curve; *BMI*, body mass index; *Cmax*, maximum serum concentration; *CVR*, contraceptive vaginal ring; *EC*, emergency contraception; *EE*, ethinyl estradiol; *ENG*, etonogestrel; *GMR*, geometric mean ratio; *HC*, hormonal contraception; *LTFU*, loss to follow up; *NET*, norethindrone; *NS*, not significant; *OC*, oral contraceptive pill; *P*, progesterone; *PD*, pharmacodynamics; *PGL*, mono-demethylated metabolite of UPA; *PK*, pharmacokinetics; *SS*, sample size; *TB*, tuberculosis; *Tmax*, time to maximum serum concentration; *UPA*, ulipristal acetate.

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