**Appendix S2.** Evidence tables

| Author, year, funding | Design | Study population | Exposures (HC, antibiotic) | Outcomes | Results | Strengths | Limitations | Quality |
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| Back (1979, 1980)<br><br>Searle, WHO, Peel Medical Trust, Mersey Health Trust. | PK<br><br>Single-sequence crossover | 8 women with TB nearing end of treatment<br><br>Ages 18-42<br>BMI not reported | COC with 50 mcg EE and 1 mg NET, single dose<br><br>Rifampin 450-600 mg/d for at least 3 months.<br><br>All on isoniazid, some also on ethambutol or pyrazinamide | EE and NET PK during and after rifampin therapy. | NET: (Rifampin, no rifampin):<br>Mean $AUC_{0-24}$: 21.9 +/- 5.9 ng/ml*h; 37.8 +/- 13.1 ng/ml*h, ($p<0.01$)<br>$t_{1/2}$: 3.2 +/- 1.0 h; 6.2 +/- 1.7 h, ($p< 0.0025$)<br><br>EE: (Rifampin, no rifampin):<br>Mean $AUC_{0-24}$: 1014 +/- 317 pg/ml*hr; 1747 +/- 218 pg/ml*hr, ($p<0.01$)<br>$t_{1/2}$: 2.9 +/- 0.8 h; 6.3 +/- 1.4 h, ($p<0.01$) | PK parameters and timing appropriate, perpetrator drug at steady state. | Not randomized, small sample size, adherence not assessed, no information on potential confounders, women had TB so uncertain generalizability | Fair |
| Barditch-Crovo (1999)<br><br>US Food and Drug Adminis-tration, National Institutes of Health | PK and clinical<br><br>Single-sequence crossover | 12 healthy women on COCs for at least 3 months<br><br>Ages 23-44<br>Median weight 61kg (43-122kg) | COC with 35 mcg EE and 1 mg NET<br><br>Rifampin 600 mg daily days 8-21 of cycle 1 or 3<br><br>Rifabutin 300 mg daily days 8-21 of cycle 1 or 3<br><br>Washout cycle between with COC only | EE and NET PK on days 7 and 21, cycle 1 and 3.<br><br>Presumed ovulation by day 21 serum P, menstrual irregularities | Rifampin:<br>EE: Mean AUC ↓ 66%, Cmax ↓ 43%, clearance ↑ two-fold, $t_{1/2}$ ↓ 48% (p for all <0.01).<br>NET: Mean AUC ↓ 51%, clearance ↑ 100%, $t_{1/2}$ ↓ 59% (p for all <0.01). No change to Cmax.<br><br>Rifabutin:<br>EE: Mean AUC ↓ 35%, clearance ↑ 53% (p <0.001). No change to Cmax, $t_{1/2}$.<br>NET: Mean AUC ↓ 13%, $t_{1/2}$↓ 18% (p for all <0.02). No change to Cmax or clearance.<br><br>No patients had elevated serum P. No pregnancies, 3 with menstrual irregularities with rifampin. | Sample size reasonable, adherence assessed by tracking caps, PK parameters and timing appropriate, basic subject characteristics provided, both drugs at steady state. | Not randomized, control and experimental draws at different times within the same cycle, rifampin not started until cycle day 8 - may have affected ovulation outcome. | Good |

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| Blode (2012)<br><br>Bayer | PK<br><br>Single-sequence crossover | 28 healthy post-menopausal women (confirmed by FSH, E2)<br><br>Ages 45-75<br>Normal BMI | COC with estradiol valerate 2mg/DNG 3mg days 1-17<br><br>Rifampicin 600mg days 12-16 1.5 hours after COC | E2V and DNG PK | E2 GMR of Cmax with/without rifampin: 75% (66.9-84.4%) and $AUC_{0-24}$ 56% (53-59%).<br>DNG: Cmax 48% (44.8-51.6%) and $AUC_{0-24}$ 17% (15.6-18.7%)<br>Steady state exposure of E2 down 44% and DNG down 83% with rifampin. | Sample size reasonable, PK parameters and timing appropriate, minimized intrasubject variability, both drugs at steady state | Not randomized, adherence not assessed, population not reproductive aged but explanation provided | Fair |
| Chen (2007)<br><br>Millen-nium Pharma-ceuticals | PK<br><br>Single sequence crossover | 14 healthy post-menopausal women<br><br>Ages 49-55<br>Mean weight 67kg (60-75kg) | COC with 35mcg EE and 1mg NET for 14 days<br><br>Single oral dose rifalazil 25mg on day 8 | EE samples on days 6 and 7, and again on days 13-14. | EE GMRs (90% CI):<br>AUC 0-24: 104.4 (99.6-109.4)<br>Cmax: 105.9 (101-111)<br>Cmin: 105 (97.7-112.8)<br>p for all >0.99 | Sample size reasonable, PK parameters appropriate, basic subject characteristics provided. | Not randomized, adherence not assessed, timing of samples was 7 days after single rifalazil dose, perpetrator drug not clearly at steady state, post-menopausal population with uncertain generalizability | Poor |
| Gupta (1988)<br><br>Funding not stated | PK<br><br>Single-sequence crossover | 6 healthy women<br><br>Ages 19-38<br>Weight 40-60kg | COC with 30mcg EE and 1mg NET during cycle 2<br><br>Single dose 450mg rifampin during control menstrual cycle and again during COC cycle | Rifampin PK | Rifampin (before COC; with COC):<br>$AUC_{0-8}$ range 29.9-176 mcg/ml/hr; 61.9-157.7 mcg/ml/hr (p>0.05)<br>Cmax range 8.2 - 36mcg/ml; 11.25-29mcg/ml (p>0.05) | PK parameters appropriate, basic subject characteristics provided, perpetrator drug at steady state. | Not randomized, small sample size, adherence not assessed, short PK follow up, timing of second rifampin dose within cycle not stated. | Poor |

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| Joshi (1980)<br><br>Schering, WHO | PK and clinical<br><br>Single-sequence crossover (PK)<br><br>Parallel (clinical) | 9 women with TB receiving non-rifampin-based therapy, (10 healthy controls for ovulation outcome only)<br><br>Ages 19-36<br>BMI not reported | COC with 30 mcg EE and 1mg NET for two cycles<br><br>Started rifampin 8-10 mg/kg daily starting during second COC cycle | EE and NET PK between days 19-23 of each cycle (n=9)<br><br>Presumed ovulation by serum P if any of two samples between days 19-23 >4ng/ml (n=7). | NET (No rifampin, with rifampin)<br>24-hour mean level (1.7 +/- 0.2 vs. 0.6 +/- 0.3, p< 0.0001)<br>AUC (127 +/- 10 vs. 89 +/- 13, p < 0.05)<br>Cmax did not change significantly.<br><br>EE: No change in mean 24 hour level, AUC or Cmax.<br><br>2 of 7 women had elevated P (> 4 ng/ml) and 3 had menstrual irregularities with rifampin but not without. | PK parameters and timing appropriate, both drugs at steady state. | Not randomized, small sample size, adherence not assessed, no information on potential confounders | Fair |
| Lebel (1998)<br><br>Ana-pharm | PK and clinical<br><br>Single-sequence crossover | 28 healthy women taking COCs for at least 2 months<br><br>Ages 18-45 years<br>BMI not reported | COC with 35 mcg EE and 1 mg NET for three cycles<br><br>Rifabutin or rifampin 300 mg daily for cycle days 1-10 during cycle 2 and 3 | EE and NET PK on day 10.<br><br>Presumed ovulation by daily serum P on days 17-19, bleeding pattern. | Rifampin vs control cycles:<br>EE AUC, Cmax, and half-life ↓ 64% 42%, and 43%, respectively<br>NET AUC, Cmax, and half-life ↓ 60%, 27%, and 58%, respectively<br><br>Rifabutin vs control cycle:<br>EE AUC, Cmax, and half-life ↓ 35%*, 20%*, and 33%, respectively<br>NET AUC, Cmax, and half-life ↓ 46%, 32% and 35%*, respectively<br><br>All decreases p<0.05<br>* = rifabutin statistically different from rifampin<br><br>No ovulatory P. More women had spotting during rifampin (36.4%) than during control cycle (3.7%). | Sample size reasonable, PK parameters and timing appropriate, both drugs at steady state. | Not randomized, adherence not assessed, no information on potential confounders. 6 subjects lost to follow up. | Good |

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| Meyer (1990)<br><br>Funding not stated | Clinical<br><br>Single sequence crossover | 22 healthy women using either IUD or vasectomy<br><br>Ages >18 years<br>BMI not reported | COC with EE 30/40/50 mcg + LNG 50/75/125 mcg during cycles 2-4<br><br>Rifampin 300mg daily during cycle 4 | Presumed ovulation if ultrasound on day 13 to showed developing follicle and day 21 serum P >10nmol/L. Inter-menstrual bleeding by diary. | All women ovulated during baseline cycle.<br>COC alone: 0/22 ovulated<br>COC + rifampin: 11/22 ovulated.<br><br>No difference in intermenstrual bleeding during three COC 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 |
| Reimers (1971)<br><br>Funding not stated | Clinical<br><br>Pro-spective cohort | 51 women with TB taking concurrent COC and TB therapy over 2-24 months<br><br>Ages and BMI not reported | Various COC formulations<br><br>Combination TB therapy containing rifampin (n=38) or no rifampin (n=13) | Bleeding pattern, disease course | Bleeding: No bleeding irregularities with non-rifampin drugs. With rifampin: 16/38 had irregular spotting or bleeding.<br><br>Disease course: TB improved when on COCs regardless of anti-TB therapy for all patients compared with historical cohort of non-COC users | | Descriptive observational study with limited information on follow up and results, variable exposures and no information on outcome assessment, no formal comparisons between groups, unblinded, no information on potential confounders | Poor |

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| Trapnell (2007)<br><br>ICON Develop-ment Solutions | PK<br><br>Single sequence crossover | 28 healthy women<br><br>Ages 18-45<br>Between -10 - 30% of ideal body weight | Single dose of 2 tablets (0.035 mg EE and 0.25 mg norgestimate) on days 0 and 14<br><br>Following 1 week washout (days 4–10), rifaximin 200 mg every 8 hours for days 11–14. | EE, NG and 17-DNGM PK<br><br>Adverse events (AE) | No differences in EE, NG, or 17-DNGM Cmax or AUC with rifaximin; bioequivalence established by 90% CI<br><br>No serious AEs and no subjects withdrew due to an AE. | Sample size reasonable, PK parameters and timing appropriate, attempted to minimize intersubject variation. | Not randomized, adherence not assessed, unclear if rifaximin at steady state - three day dose may not have full enzyme induction effect. | Fair |

Abbreviations: WHO World Health Organization; PK pharmacokinetic; BMI body mass index; TB tuberculosis; COC combined oral contraceptive; EE ethinyl-estradiol; NET norethindrone; AUC area under the curve; $t_{1/2}$ half-life; US United States; P progesterone; Cmax maximum serum concentration; FSH follicle stimulating hormone; E2 estradiol; DNG dienogest; E2V estradiol valerate; GMR geometric mean ratio; CI confidence interval; IUD intrauterine device; LNG levonorgestrel; NG norgestimate; 17-DNGM 17-deacetyl norgestimate.