

Drug Interactions Between Rifamycin Antibiotics and Hormonal Contraceptives: A Review**Rahul Kumhar¹, Ishita Meghwal¹, Jitendra Choudhary¹, Kamlesh Gehlot¹, Vinod¹, Arfa Khan², Anshika Chouhan²**¹Students, Sunrise College of Pharmacy, Udaipur, Rajasthan, India²Assistant Professors, Sunrise College of Pharmacy, Udaipur, Rajasthan, India

Received: 10-01-2026 / Revised 16-02-2026 / Accepted 22-03-2026

Corresponding author: Dr. Arfa Khan

Conflict of interest: Nil

Abstract:

Hormonal contraceptives may be affected by concomitant medicines that alter steroid-hormone metabolism. Rifamycin antibiotics are particularly important because some members of this class, especially rifampicin (rifampin), strongly induce drug-metabolizing enzymes and can reduce systemic exposure to contraceptive hormones. This review summarizes pharmacokinetic, pharmacodynamic, clinical, and guideline evidence concerning interactions between rifamycin antibiotics and hormonal contraceptives. Evidence is strongest for combined oral contraceptives (COCs), for which rifampicin has been associated with reductions in ethinyl estradiol and progestin exposure and, in some studies, increased markers of ovarian activity. Rifabutin also alters contraceptive pharmacokinetics, but generally to a lesser extent than rifampicin. Evidence concerning etonogestrel implants has expanded: rifampicin reduces serum etonogestrel concentrations and has been associated with altered ovarian-activity biomarkers, and a published case report described pregnancy during concomitant rifampicin therapy. Evidence for non-oral systems is more heterogeneous. A 2025 study of a sequesterone acetate/ethinyl estradiol vaginal contraceptive system found reduced ethinyl estradiol exposure but no significant change in sequesterone acetate exposure, illustrating why interactions should be assessed for the specific contraceptive formulation. Rifaximin and rifalazil have not demonstrated clinically important pharmacokinetic effects on ethinyl estradiol in the studies reviewed. Clinical management should therefore consider the individual rifamycin, contraceptive formulation, duration of therapy, and current contraceptive guidance rather than treating all rifamycins as interchangeable.

Keywords: Rifamycin Antibiotics; Rifampicin; Rifabutin; Hormonal Contraceptives; Drug–Drug Interactions; Pharmacokinetics; Contraceptive Efficacy; Enzyme Induction.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Hormonal contraception includes combined estrogen–progestin methods and progestin-only methods delivered by oral, transdermal, vaginal, injectable, or implantable routes. Contraceptive effectiveness depends, among other factors, on adequate exposure to the active steroid hormones. Concomitant medicines that increase hormone clearance can therefore alter systemic exposure and potentially compromise contraceptive effectiveness.

Rifamycin antibiotics are widely used in the treatment of tuberculosis and other mycobacterial infections. Rifampicin is a potent inducer of drug-metabolizing enzymes and transport pathways and is consequently capable of lowering exposure to several medicines, including steroid hormones. A systematic review found that rifampicin reduced estrogen and/or progestin exposure in multiple studies, while evidence for actual pregnancy outcomes was historically limited. [1]

Subsequent research has expanded the evidence base to etonogestrel implants and non-oral hormonal systems. Rifampicin has been shown to reduce serum etonogestrel concentrations and alter biomarkers of ovarian activity, while a 2022 case report described pregnancy during rifampicin-based tuberculosis treatment in an etonogestrel implant user. [2,4] A 2025 pharmacokinetic study of a sequesterone acetate/ethinyl estradiol vaginal contraceptive system further demonstrated that the magnitude and clinical interpretation of an interaction may depend on the specific formulation. [5]

The objective of this review is to summarize the available evidence on rifamycin–hormonal contraceptive interactions, describe the underlying pharmacokinetic mechanisms, compare individual rifamycins, and highlight clinically relevant evidence gaps.

Hormonal Contraceptive Methods and Evidence of Interaction

Combined Oral Contraceptives: Combined oral contraceptives contain an estrogen and a progestin. Their interaction with rifampicin and rifabutin has been evaluated primarily through pharmacokinetic and pharmacodynamic studies. Rifampicin has been associated with lower systemic exposure to ethinyl estradiol and norethisterone/norethindrone. In a controlled crossover study, rifampicin reduced ethinyl estradiol AUC_{0-24} by 64% and C_{max} by 42%, while norethindrone AUC_{0-24} decreased by 60%; the corresponding reductions with rifabutin were smaller. [3]

Older studies also demonstrated shortened hormone half-lives and reduced exposure during rifampicin treatment. These findings provide a pharmacokinetic basis for concern about reduced contraceptive effectiveness when rifampicin or rifabutin is used with combined hormonal contraception. [7–10]

Progestin-Only Contraceptives: Evidence for progestin-only contraception is less extensive than for COCs but has increased in recent years. In etonogestrel implant users, rifampicin significantly

reduced serum etonogestrel concentrations and altered biomarkers of ovarian activity. [2] A published case report described an unplanned second-trimester pregnancy in an etonogestrel implant user receiving rifampicin-based antituberculosis therapy. A single case cannot establish the frequency of contraceptive failure, but it provides clinically relevant evidence that the interaction may have consequences beyond pharmacokinetic measurements. [4]

Non-Oral Hormonal Contraceptives: Evidence for non-oral hormonal methods is heterogeneous and should not be generalized across formulations. A 2025 randomized crossover study evaluated a contraceptive vaginal system releasing segesterone acetate and ethinyl estradiol during rifampin treatment. Rifampin significantly reduced ethinyl estradiol exposure, whereas segesterone acetate exposure remained within bioequivalence limits. The investigators concluded that the specific vaginal system studied was not expected to lose contraceptive effectiveness with rifampin. [5] This finding illustrates that a pharmacokinetic change in one hormone does not necessarily translate into contraceptive failure and that formulation-specific evidence is important.

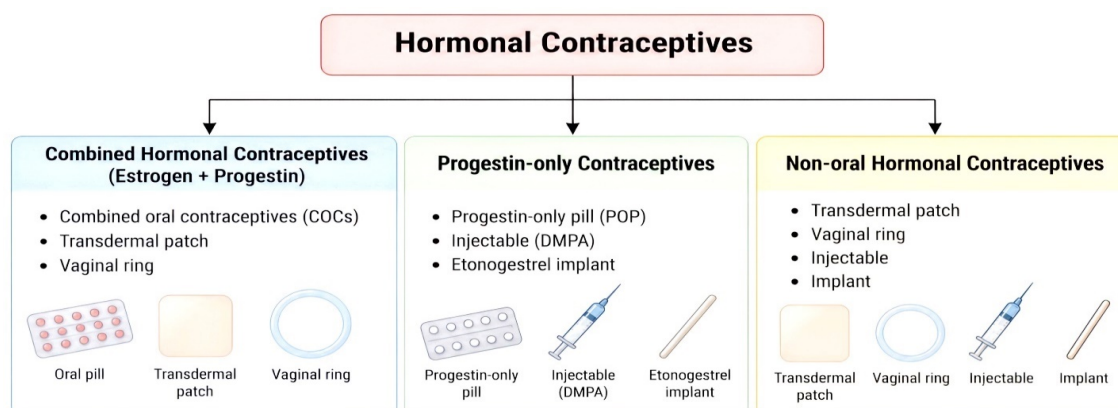


Figure 1. Classification of hormonal contraceptives.

Figure 1: Schematic classification of hormonal contraceptive methods.

Rifamycin Antibiotics

Rifampicin (Rifampin): Rifampicin is the best-characterized rifamycin in the context of hormonal contraception. It is a strong inducer of hepatic drug-metabolizing enzymes and can increase the clearance of steroid hormones. Studies involving COCs consistently demonstrate reductions in estrogen and/or progestin exposure, and newer evidence shows reduced etonogestrel exposure in implant users. [1–3,7–10]

Rifabutin: Rifabutin also induces drug-metabolizing enzymes but generally produces smaller pharmacokinetic changes than rifampicin. In the randomized crossover study by LeBel et al.,

reductions in ethinyl estradiol and norethindrone exposure were less pronounced with rifabutin than with rifampicin. [3] Current contraceptive guidance nevertheless treats rifabutin as clinically relevant because reduced effectiveness may occur with some hormonal methods. [6]

Rifapentine: Direct evidence concerning rifapentine and hormonal contraception is limited compared with rifampicin and rifabutin. Consequently, conclusions about contraceptive effectiveness should be made cautiously and with reference to current clinical guidance and the specific contraceptive method. [1,6]

Rifaximin and Rifalazil: Rifaximin has limited systemic absorption and did not alter the pharmacokinetics of ethinyl estradiol or norgestimate metabolites in a controlled study. [12] Rifalazil likewise did not significantly alter ethinyl

estradiol pharmacokinetics in the evaluated study. [11] These findings should not be extrapolated to systemically administered rifamycins with strong enzyme-inducing activity.

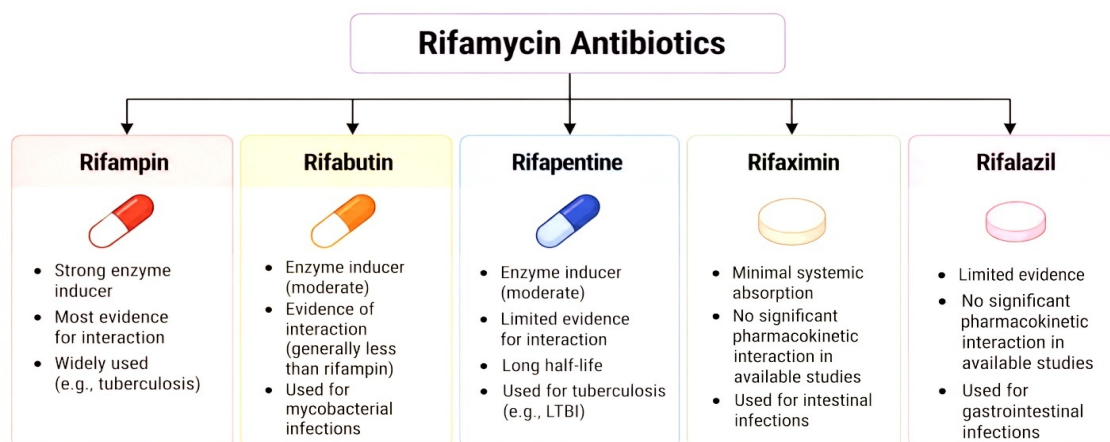


Figure 2. Classification of rifamycin antibiotics.

Figure 2: Rifamycin antibiotics and the relative extent of available evidence concerning hormonal contraceptive interactions.

Mechanisms of Rifamycin–Hormonal Contraceptive Interaction

CYP-Mediated Enzyme Induction: The principal mechanism for the interaction with rifampicin is induction of drug-metabolizing enzymes, including CYP3A-mediated pathways. Increased metabolic activity can accelerate the clearance of contraceptive steroids and reduce systemic exposure. Classic pharmacokinetic studies demonstrated shortened ethinyl estradiol half-life and increased oxidative metabolism during rifampicin treatment. [10]

Reduction in Hormonal Exposure: Reduced exposure may be reflected by lower AUC, lower C_{max} , shorter elimination half-life, and lower circulating hormone concentrations. The magnitude of change varies with the hormone, contraceptive

formulation, rifamycin, dose, and duration of exposure. [3,7–10]

Pharmacokinetic and Pharmacodynamic Consequences: Pharmacokinetic changes do not automatically prove contraceptive failure. Pharmacodynamic outcomes such as ovulation or ovarian-activity biomarkers provide additional information about whether reduced hormone exposure is biologically consequential. The available literature shows that rifampicin can alter ovarian-activity markers in some settings, while not every pharmacokinetic change has been accompanied by observed ovulation or pregnancy. [1–3]

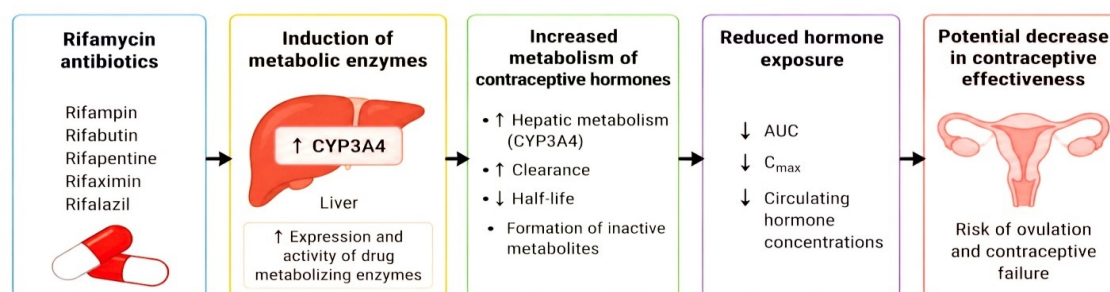


Figure 3. Mechanism of rifamycin–hormonal contraceptive interaction.

Figure 3: Proposed mechanism of rifamycin-associated reduction in systemic exposure to hormonal contraceptives.

Evidence from Individual Studies: The evidence base includes controlled pharmacokinetic studies, pharmacodynamic assessments, a systematic review, and clinical case evidence. The 2018 systematic review identified 11 eligible studies and found that rifampicin reduced estrogen and/or progestin exposure in several studies and increased the frequency of ovulation in some studies; however, the included studies did not report pregnancy rates. [1]

LeBel et al. directly compared rifampicin and rifabutin in 28 healthy premenopausal women receiving a combined oral contraceptive. Rifampicin produced larger reductions in ethinyl estradiol and norethindrone exposure than rifabutin. [3] Subsequent work in etonogestrel implant users showed reduced serum etonogestrel concentrations and altered ovarian-activity biomarkers during rifampicin administration. [2]

Clinical evidence remains limited but includes a published case of pregnancy in an etonogestrel implant user receiving rifampicin-based tuberculosis therapy. [4] For non-oral contraception, the 2025 vaginal-system study provides an important formulation-specific example: rifampin reduced ethinyl estradiol exposure but did not significantly change sequesterone acetate exposure. [5]

Pharmacokinetic Evidence: The principal pharmacokinetic measures reported across studies are AUC, C_{max}, circulating hormone concentration, clearance, and elimination half-life. These parameters consistently show that rifampicin can increase steroid-hormone clearance and reduce exposure for several oral contraceptive formulations. [3,7–10]

Effect on AUC: Rifampicin substantially reduces the AUC of ethinyl estradiol and several progestins

in the evaluated COC studies. In the LeBel et al. study, ethinyl estradiol AUC_{0–24} decreased by 64% and norethindrone AUC_{0–24} by 60%. The corresponding decreases with rifabutin were 35% and 20%, respectively. [3]

Effect on C_{max} and Hormone Concentrations: Rifampicin can reduce peak and circulating concentrations of contraceptive hormones. In the LeBel study, ethinyl estradiol C_{max} decreased by 42% with rifampicin and by 20% with rifabutin. [3]

Effect on Progestin Exposure: Rifampicin reduces exposure to several progestins used in oral contraception and lowers serum etonogestrel concentrations in implant users. [2,3,8] The clinical relevance of the change depends on the contraceptive formulation and the degree to which contraceptive efficacy depends on the affected hormone.

Rifampicin Compared with Rifabutin: Both rifampicin and rifabutin can alter contraceptive hormone pharmacokinetics, but the magnitude of change is generally greater with rifampicin. [3] Current guidance therefore considers both drugs relevant to contraceptive management, while recognizing differences between specific methods. [6]

Other Rifamycin Derivatives: Rifaximin and rifalazil did not demonstrate significant pharmacokinetic effects on ethinyl estradiol in the evaluated studies. [11,12] Evidence for rifapentine is more limited. [1,6]

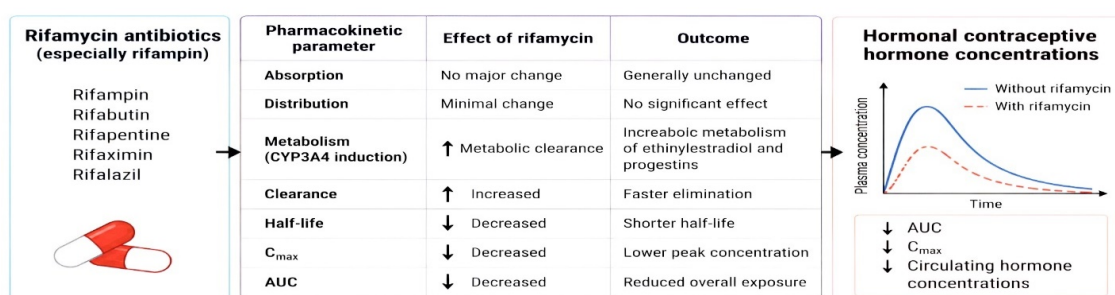


Figure 4. Pharmacokinetic effects of rifamycin on hormonal contraceptives.

Figure 4: Schematic representation of pharmacokinetic effects reported with rifamycin–hormonal contraceptive combinations.

Ovulation and Contraceptive Effectiveness: A reduction in hormone concentration is a pharmacokinetic finding and should not be equated automatically with contraceptive failure. The relationship between reduced exposure, ovarian activity, ovulation, and pregnancy is complex. The systematic review by Simmons et al. reported increased ovulation frequency in some rifampicin studies, but the included studies did not provide pregnancy-rate estimates. [1]

In etonogestrel implant users, rifampicin reduced serum etonogestrel concentrations and changed biomarkers of ovarian activity. [2] The subsequent case report of pregnancy during rifampicin therapy provides clinical evidence consistent with the possibility of reduced implant effectiveness, although a single case cannot quantify the risk. [4]

For the segesterone acetate/ethinyl estradiol vaginal system studied in 2025, rifampin reduced ethinyl estradiol exposure without significantly affecting segesterone acetate exposure, and the study authors did not expect reduced contraceptive effectiveness for that specific system. [5] This formulation-specific result reinforces the need to distinguish

pharmacokinetic effects from demonstrated clinical failure.

Clinical Outcomes and Safety Considerations:

The literature contains more pharmacokinetic and pharmacodynamic evidence than direct pregnancy-outcome evidence. Clinically, the most important concern is unintended pregnancy when a strong enzyme-inducing rifamycin is combined with a hormonal contraceptive whose effectiveness depends on adequate systemic steroid exposure. [1,4]

Current U.S. Medical Eligibility Criteria guidance states that rifampin or rifabutin therapy can reduce the effectiveness of combined hormonal contraceptives and certain progestin-only methods. For long-term use, other contraceptive options are encouraged; depot medroxyprogesterone acetate is treated differently because its effectiveness is not reduced by rifampin or rifabutin. [6] These recommendations should be applied alongside local and national guidance and the characteristics of the individual patient and contraceptive method.

Comparison of Rifamycins

Table 1: Summary of evidence on rifamycin–hormonal contraceptive interactions and their clinical significance.

Rifamycin	Evidence for interaction	Main evidence	Clinical interpretation
Rifampicin (rifampin)	Strongest evidence	Reduced COC hormone exposure; reduced etonogestrel concentrations; altered ovarian-activity markers; clinical case report	Clinically important interaction; method-specific management required [1–4,6]
Rifabutin	Moderate evidence	Reduced ethinyl estradiol and norethindrone exposure, generally less than rifampicin	Potentially clinically relevant; consult current guidance [3,6]
Rifapentine	Limited evidence	Few direct hormonal-contraception studies	Avoid extrapolation from rifampicin without guidance [1,6]
Rifaximin	Limited but reassuring PK evidence	No significant change in EE/norgestimate PK in a controlled study	No significant interaction demonstrated in the evaluated study [12]
Rifalazil	Limited but reassuring PK evidence	No significant change in EE PK in the evaluated study	No significant interaction demonstrated in the evaluated study [11]

Table 1. Summary of the published evidence on interactions between individual rifamycins and hormonal contraceptives. The strength of evidence

reflects the amount and type of available evidence rather than a formal evidence-grading system.

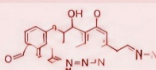
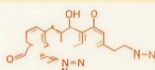
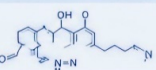
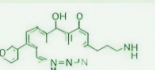
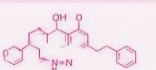
Comparison of rifamycins and evidence for interaction with hormonal contraceptives					
Rifamycin	Rifampin	Rifabutin	Rifapentine	Rifaximin	Rifalazil
Structure (simplified)					
Enzyme induction potential	Strong	Moderate	Moderate (limited data)	Minimal (low systemic absorption)	Unknown / Limited
Evidence for interaction with hormonal contraceptives	Consistent evidence of reduced hormone concentrations and contraceptive effectiveness	Evidence of interaction (generally smaller effect than rifampin)	Limited evidence	No significant pharmacokinetic interaction in available studies	No significant interaction in available studies
Effect on hormone exposure (AUC, C _{max})	↓ AUC, ↓ C _{max}	↓ AUC, ↓ C _{max} (smaller reduction)	↓ AUC, ↓ C _{max} (limited data)	Generally unchanged	Generally unchanged (limited data)
Clinical relevance	High risk of contraceptive failure	Possible reduced effectiveness	Uncertain (clinical significance not well established)	Low risk	Low risk (limited data)
Common use	Tuberculosis, leprosy and other infections	Mycobacterial infections (e.g., MAC)	Tuberculosis (LTBI)	Gastrointestinal infections	Gastrointestinal infections

Figure 5. Comparison of rifamycins and evidence for interaction with hormonal contraceptives.

Figure 5: Comparative schematic of rifamycins and the available evidence concerning hormonal contraceptive interactions.

Current Clinical Recommendations: Contraceptive management during rifamycin therapy should be based on the individual rifamycin, the contraceptive formulation, and the expected duration of therapy. Rifampicin and rifabutin are the most clinically important enzyme-inducing agents in this context. [6]

For patients receiving long-term rifampicin or rifabutin, current U.S. guidance recommends considering alternative contraceptive methods because combined hormonal contraceptive effectiveness may be reduced and certain progestin-only methods may also be affected. Depot medroxyprogesterone acetate is classified differently because its effectiveness is not decreased by rifampin or rifabutin. [6] Decisions should also take into account local guidelines, patient preferences, contraindications, and access to alternative contraception.

The evidence should be communicated carefully: a pharmacokinetic interaction does not always prove clinical contraceptive failure, and findings from one formulation should not automatically be generalized to another. The 2025 segesterone acetate/ethinyl estradiol vaginal-system study is an example of why formulation-specific evidence matters. [5]

Evidence Gaps and Limitations

- The evidence base is uneven across rifamycins and contraceptive formulations. Rifampicin has substantially more evidence than rifapentine and several other derivatives. [1,6]
- Many studies are small pharmacokinetic investigations, and direct pregnancy outcomes are less frequently measured than AUC, C_{max}, hormone concentrations, or ovarian biomarkers. [1]

- Evidence for implants and other non-oral systems is still developing. Although recent studies have improved the evidence base, clinical outcome data remain limited. [2,4,5]
- Results from one contraceptive formulation should not be extrapolated automatically to another because hormone composition, route of administration, and dependence on individual hormones can differ.
- Further research should integrate pharmacokinetic measures with ovulation and pregnancy outcomes and should evaluate commonly used contraceptive formulations with individual rifamycin agents.

Conclusion

Rifamycin antibiotics can interact with hormonal contraceptives, with the strongest and most consistent evidence involving rifampicin. Rifampicin can substantially reduce systemic exposure to several contraceptive estrogens and progestins and can affect ovarian-activity measures in some contraceptive settings. Rifabutin also produces pharmacokinetic changes, generally of smaller magnitude than rifampicin. [1–3]

Clinical evidence of contraceptive failure remains more limited than pharmacokinetic evidence, although pregnancy has been reported in an etonogestrel implant user receiving rifampicin. [4] Conversely, recent formulation-specific evidence from a segesterone acetate/ethinyl estradiol vaginal system demonstrates that a reduction in one hormone's exposure does not necessarily imply reduced contraceptive effectiveness. [5]

Accordingly, the interaction should be evaluated according to the specific rifamycin, contraceptive formulation, duration of treatment, and current clinical guidance. Further well-designed studies

linking pharmacokinetic changes with ovarian activity and pregnancy outcomes are needed, particularly for less-studied rifamycins and non-oral contraceptive methods.

Abbreviations

AUC – area under the concentration–time curve; **CHC** – combined hormonal contraceptive; **COC** – combined oral contraceptive; **C_{max}** – maximum plasma concentration; **CYP** – cytochrome P450; **EE** – ethinyl estradiol; **HC** – hormonal contraception; **PK** – pharmacokinetics; **PD** – pharmacodynamics; **SA** – segesterone acetate.

References

1. Simmons KB, Haddad LB, Nanda K, Curtis KM. Drug interactions between rifampicin antibiotics and hormonal contraception: a systematic review. *BJOG*. 2018;125(7):804–811. doi:10.1111/1471-0528.15027.
2. Lazorwitz A, Sheeder J, Teal S. The effect of rifampin on serum etonogestrel concentrations and biomarkers of ovulation among contraceptive implant users: a pharmacokinetic and pharmacodynamic study. *Contraception*. 2023;123:110035. doi:10.1016/j.contraception.2023.110035.
3. LeBel M, Masson E, Guilbert E, Colborn D, Paquet F, Allard S, Vallée F, Narang PK. Effects of rifabutin and rifampicin on the pharmacokinetics of ethinylestradiol and norethindrone. *J Clin Pharmacol*. 1998;38(11):1042–1050. doi:10.1177/009127009803801109.
4. Tufa TH, Fessehay A, Abubeker FA. Etonogestrel contraceptive implant failure in a woman taking rifampin: a case report. *Contracept Reprod Med*. 2022;7:5. doi:10.1186/s40834-022-00172-1.
5. Plagianos M, Lansiaux M, Kumar N, Graham S, Sussman H, Kushner H, Creasy G, Bernick B, Haddad LB. A drug-drug interaction study to evaluate the effects of strong CYP3A4 inducer on the pharmacokinetics of segesterone acetate and ethinyl estradiol in a contraceptive vaginal system. *Contracept Reprod Med*. 2025;10:78. doi:10.1186/s40834-025-00414-y.
6. Centers for Disease Control and Prevention. U.S. Medical Eligibility Criteria for Contraceptive Use, 2024. *MMWR Recomm Rep*. 2024;73(4).
7. Back DJ, Breckenridge AM, Crawford FE, Hall JM, MacIver M, Orme ML, Rowe PH, Smith E, Watts MJ. The effect of rifampicin on the pharmacokinetics of ethinylestradiol in women. *Contraception*. 1980;21(2):135–143. doi:10.1016/0010-7824(80)90125-0.
8. Back DJ, Breckenridge AM, Crawford F, MacIver M, Orme ML, Park BK, Rowe PH, Smith E. The effect of rifampicin on norethisterone pharmacokinetics. *Eur J Clin Pharmacol*. 1979;15(3):193–197. doi:10.1007/BF00563105.
9. Joshi JV, Joshi UM, Sankolli GM, Gupta K, Rao AP, Hazari KT, Sheth UK, Saxena BN. A study of interaction of a low-dose combination oral contraceptive with anti-tubercular drugs. *Contraception*. 1980;21(6):617–629. doi:10.1016/0010-7824(80)90034-7.
10. Bolt HM, Bolt M, Kappus H. Interaction of rifampicin treatment with pharmacokinetics and metabolism of ethinylestradiol in man. *Acta Endocrinol (Copenh)*. 1977;85(1):189–197. doi:10.1530/acta.0.0850189.
11. Chen YX, Cabana B, Kivel N, Pieniaszek H, Gilman S, Michaelis A. Lack of effect of rifalazil on ethinyl estradiol pharmacokinetics in healthy postmenopausal women. *Int J Clin Pharmacol Ther*. 2007;45(7):418–422. doi:10.5414/CPP45418.
12. Trapnell CB, Connolly M, Pentikis H, Forbes WP, Bettenhausen D. Absence of effect of oral rifaximin on the pharmacokinetics of ethinyl estradiol/norgestimate in healthy females. *Ann Pharmacother*. 2007;41(2):222–228. doi:10.1345/aph.1H395.