THE DENTAL CLINICS OF NORTH AMERICA

Dent Clin N Am 46 (2002) 653–664

Antibiotics and oral contraceptives

Scott S. DeRossi, DMD[a],
Elliot V. Hersh, DMD, MS, PhD[b,*]

[a]*Department of Oral Medicine, University of Pennsylvania School of Dental Medicine, 4001 Spruce Street, Philadelphia, PA 19104-6003, USA*
[b]*Department of Oral Surgery and Pharmacology, University of Pennsylvania School of Dental Medicine, 4001 Spruce Street, Philadelphia, PA 19104-6003, USA*

Oral contraceptives and antibiotics are among the most widely used prescription medications in the United States. It is estimated that more than 11 million women in the United States use oral contraceptives, with up to 70 million women worldwide. Many more women of childbearing potential also periodically consume antibiotics. The proposed interaction between oral contraceptives and antibiotics has long been a major source of controversy and discussion in the literature [1]. Antibiotics are alleged to reduce blood concentrations and, therefore, the ultimate effectiveness of oral contraceptive agents. The proposed mechanisms of these antibiotic-associated interactions include hepatic microsomal enzyme induction by the antibiotic of both the estrogen and progestin components of the oral contraceptive, interference with enterohepatic circulation of the oral contraceptive metabolites, interference with oral contraceptive absorption from the gastrointestinal tract, alterations in plasma-protein binding of the oral contraceptive components, and increased excretion of the oral contraceptive. Considering the relatively high usage of both antibiotics and oral contraceptives, there is little scientific evidence to support this interaction. But sporadic case reports of oral contraceptive failure during concomitant antibiotic therapy do appear in the literature, and, to fully understand the rationale behind the proposed interaction, a discussion of the pharmacology of oral contraceptives is necessary.

* Corresponding author.
E-mail address: evhersh@pobox.upenn.edu (E.V. Hersh).

PII: S0011-8532(02)00017-4

The pharmacology of oral contraceptives

There are three types of oral contraceptives:

(1) The combined fixed-dose estrogen-progestin preparations (with high, medium, or low estrogen content)
(2) The combined sequential preparations with the doses of each steroid varied throughout the menstrual cycle
(3) The progestin-only preparations.

The goal of oral contraceptive therapy is to use a preparation that will minimize complications and side effects yet still prevent pregnancy.

Oral steroid contraceptives, or combination pills, are a mixture of semi-synthetic estrogens, usually ethinyl estradiol (EE) or mestranol, and semi-synthetic progesterones known as progestins (eg, norethindrone, levonorgestrel). In general, the estrogen component of oral contraceptives blocks ovulation by inhibiting the release of follicle-stimulating hormone (FSH) and leutinizing hormone (LH) via negative feedback on the pituitary gland and hypothalamus. The progestin component of oral contraceptives increases the viscosity of the cervical fluid, changes the endometrial lining to make it unsuitable for egg implantation, and provides some antiovulatory action [2,3].

To be effective, oral contraceptives must have adequate circulating concentrations of active hormone to prevent ovulation. In general, estrogens are present in very low concentrations (pg/ml) and sensitive and specific assays have only recently become available. Through these assays, it has become evident that even without any significant drug interactions, there is tremendous variation in plasma concentrations of active hormone among women. It is likely that women who have the lowest concentrations of estrogen are most likely to suffer interactions with other drugs.

Though it is the most effective form of reversible contraception, oral contraceptives, like any medication, are not 100% effective, and many women conceive while taking these preparations. When taken correctly, they reduce the chance of pregnancy to less than 1%. The reported failure rate among United States women is approximately 3% [4]. In the teenage population, the failure rate can be as high as 8%, often attributed to missed doses [5]. The most common causes of the pregnancies are thought to be missed pills, malabsorption, and drug interactions.

Oral contraceptives are not without side effects. The most critical side effect of the estrogen component is an increased risk of venous throboembolytic disease. The progestin component has been associated with increases in blood pressure, serum glucose, and serum lipid levels. An increased risk of myocardial infarction and stroke has been reported in oral contraceptive users who smoke and are greater than 35 years of age [6]. These significant adverse effects have led to the development of pills with reduced dosages of both estrogen and progestin components.

Interactions with rifampin

In the 1970s, reports began to appear regarding drug interactions between oral contraceptives and the antituberculosis drug rifampin. This was the first antibiotic implicated in reducing the effectiveness of oral contraceptives. Reimers and Jezek reported that 38 of 51 women (75%) taking rifampin and oral contraceptives concomitantly experienced breakthrough bleeding, an indicator of ovulation [7]. Two years later, another report of 88 women on oral contraceptive therapy associated concomitant rifampin use with 66 instances of breakthrough bleeding and five pregnancies [8]. Since then, other reports have followed associating increased risk of pregnancy with concomitant use of rifampin and oral contraceptives. Not surprisingly, over three-quarters of all alleged antibiotic–oral contraceptive interactions involve rifampin [9]. Clinical studies clearly demonstrate that rifampin significantly reduces blood levels of both the estrogen and progestin components of oral contraceptives [10–12] (Fig. 1). Though short-term exposure to rifampin or the related drug rifabutin may result in increased ethinyl estradiol and norethindrone clearance without reversing their contraceptive effect [12], long-term administration of these agents for tuberculosis therapy or prophylaxis is associated with both a diminution of hormonal blood levels and a reduction in contraceptive efficacy [7–11].

Rifampin is a potent inducer of the liver cytochrome p450 system and results in the increased metabolism and subsequent diminished blood levels of a number of drugs, including oral contraceptives [13]. Among antibiotics, only rifampin has been scientifically demonstrated to reduce blood levels and interfere with the effectiveness of oral contraceptives.

Interactions with other antibiotics

Anecdotal evidence implicating more commonly prescribed antibiotics with interference of oral contraceptive effectiveness began appearing in 1975. Dosseter reported three cases of pregnancy in patients taking oral contraceptives who were given ampicillin [14]. A few years later, another report was published describing a 20-year-old student who claimed to be totally compliant with her oral contraceptive regimen but became pregnant after a 5-day course of tetracycline [15]. In 1982, DeSano and Hurley described 16 pregnancies over a 2-year period in their private obstetric/gynecologic practices, all in patients who claimed to be compliant with their contraceptive regimen [16]. Antibiotics had been consumed in 13 of the cases; 5 patients had reported using ampicillin, 3 patients used penicillin, 3 patients had used sulfisoxazole or another sulfonamide antibiotic, 1 patient had used tetracycline, and 1 patient had used cephalexin. In 1986, a case report of an alleged antibiotic–oral contraceptive interaction appeared in the dental literature. Bainton reported a case of a 19-year-old who had taken an oral contraceptive for 18 months and received an intramuscular injection of a

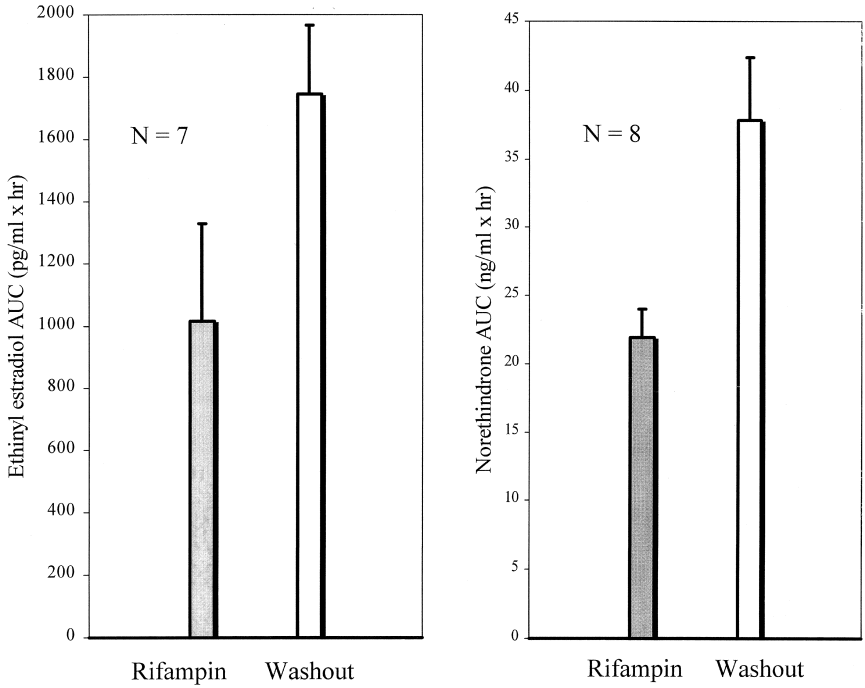

Fig. 1. Effects of rifampin on blood levels of ethinyl estradiol and norethindrone. Women received daily doses of 450–600 mg rifampin for up to 1 year from exposure to tuberculosis, followed by a 1-month washout period. A single dose of Minovlar® (50 ug ethinyl estradiol plus 1 mg norethindrone acetate) was administered after an overnight fast, toward the end of rifampin therapy and again 1 month after discontinuing rifampin. Blood samples for pharmacokinetic analyses were taken immediately before Minovlar® ingestion and then at 1, 2, 3, 4, 6, 8, 11, 14, and 24 hours after dosing. There was a significant decrease in area under the plasma concentration curves (mean ± SE) for both ethinyl estradiol ($p < 0.01$) and norethindrone ($p < 0.01$) during rifampin therapy compared with the control washout period as analyzed by Student t tests. (*Adapted from* Back DJ, Breckenridge AM, Crawford FE, et al. The effect of rifampicin on the pharmacokinetics of ethinyl estradiol in women. Contraception 1980;21(2):135–43; and Back DJ, Breckenridge AM, Crawford FE, et al. The effect of rifampicin on norhisterone pharmacokinetics. Eur J Clin Pharmacol 1979;15:193–7; with permission.)

long-acting penicillin combination during a surgical extraction procedure [17]. Three months later, she was found to be pregnant with twins.

Back et al published the most comprehensive report of potential antibiotic–oral contraceptive interactions [18]. They gathered data from the United Kingdom's Committee on Safety in Medicines between 1968 and 1984. During this time, 63 pregnancies were reported with simultaneous administration of oral contraceptives and antibiotics, excluding rifampin. Penicillins were implicated in 32 of these pregnancies, tetracyclines in 12, cotrimoxazole (sulfamethoxazole and trimethoprim) in 5, metronidazole in 3, erythromycin

in 2, cephalosporins in 2, and either ''unknown antibiotics'' or antibiotics not commonly used in dentistry in the other 7 cases. In an effort to temper these findings, they also reported, that there were over 307 million prescriptions for these same antibiotics, and approximately 2.5 million regular users of oral contraceptives during this time period. Based on these figures, the actual number of reported pregnancies in England alleged to involve oral contraceptive interactions with antibiotics other than rifampin was extremely low.

In the United States, 29 reports of unintended pregnancies in oral contraceptive users who received penicillins or tetracyclines were listed in the United States Department of Health and Human Services' MEDWATCH Spontaneous Reporting System [19]. These numbers also should be tempered with the fact that over 11 million women per year use oral contraceptives in the United States [1].

The pharmacological basis of the interaction

A number of theories have been proposed to explain the occasional failures seen in oral contraceptive effectiveness when antibiotics are concomitantly ingested. The evidence-based support or ''better, lack of support'' for each theory is briefly reviewed below.

Hepatic microsomal enzyme induction

A number of drugs are capable of inducing liver microsomal enzymes, thereby increasing the rate of metabolism of both themselves and other drugs. This is certainly the case with rifampin, a potent inducer of the liver microsomal enzyme system. When ingested by women who are also oral contraceptive users, circulating estrogen and progestin concentrations may drop dramatically, below levels necessary to prevent ovulation. Decreased oral contraceptive effectiveness has been described with the concurrent use of other drugs known to induce microsomal enzymes, such as anticonvulsants and barbiturates [18,20]. None of the antibiotics currently used in outpatient dentistry, however, are liver microsomal enzyme inducers.

Interference with enterohepatic circulation of steroid metabolites

The ability of antibiotics to inhibit the enterohepatic recirculation of the estrogen component of oral contraceptives is probably the most widely promulgated theory of oral contraceptive failure. Ethinyl estradiol (EE) is well absorbed in humans, but the bioavailability of EE is approximately 40–50% because of a large first-pass metabolism in the gut and liver. Some of these inactive metabolites are sulfate and glucuronic acid conjugation products, which are subsequently excreted in the bile [21]. It is thought that these conjugates are then hydrolyzed by gut colonic bacteria, liberating the

lipid-soluble and active parent compound, which is readily absorbed from the intestine into the bloodstream, providing the necessary additional serum concentrations to prevent ovulation (Fig. 2). This enterohepatic recirculation would be far more important for EE than for progestins because the latter undergoes significant phase 1 oxidative metabolism prior to conjugation. In theory, antibiotics that kill or inhibit the growth of the colonic bacteria involved in the deconjugation of EE can inhibit the enterohepatic recirculation of the active estrogen component. Animal studies do support the enterohepatic recirculation theory [22], but studies in humans fail to document the same interference. Some experts have speculated that there may be a subset of women that rely more heavily on enterohepatic recirculation of EE to maintain therapeutic serum levels. An atypical gut flora, which is highly sensitive to the administered antibiotic and/or a defective cytochrome p450 isoenzyme system where phase 2 metabolism (glucoronidation and sulfation) of the parent EE molecule is more heavily relied upon than initial phase 1 hydroxylation reactions, may contribute to this phenomena and the subsequent reduction in antiovulatory estrogen blood levels [22–24].

Interference with absorption from the gastrointestinal tract

There have been few studies concerning the absolute bioavailability of EE. Indirect evidence exists that EE is rapidly absorbed with the peak plasma concentration achieved at 120 minutes after dosing [24]. Interference with oral contraceptive absorption from the gastrointestinal tract has been demonstrated with ascorbic acid, but to date no interactions with antibiotics through this mechanism have been reported. Infective diarrhea because of increased gastrointestinal motility might reduce oral contraceptive

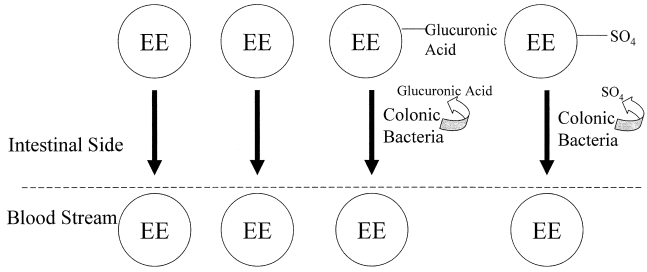

Fig. 2. Proposed action of colonic bacteria on the disposition of ethinyl estradiol (EE). EE undergoes a significant first-pass effect, and some of these inactive metabolites are conjugates of glucuronic acid and SO_4. These conjugated metabolites of EE would be inactive and lack sufficient lipid solubility to be absorbed into the blood stream, leading to a diminution of EE blood levels. It is hypothesized that bacteria, which are part of the normal intestinal flora, cleave the glucuronic acid and SO_4 groups from the metabolized EE molecules, liberating the active and lipid-soluble parent molecule that can be reabsorbed into the blood stream. By killing or inhibiting the growth of the normal intestinal microflora, antibiotics may interfere with this recycling process and result in the reduction of EE blood levels.

absorption. Although antibiotics can induce diarrhea, there are no published reports of such an event reducing the effectiveness of oral contraceptive agents.

Alterations in plasma protein binding

Ethinyl estradiol is 97% bound to plasma proteins, namely albumin, and plays a role in sex hormone-binding globulin capacity. As synthetic progestins are carried by sex hormone-binding globulin, various ratios of ingested hormones may produce alterations in binding, leading to significant changes in total plasma hormone concentrations. In general, protein-binding drug interactions are overemphasized for most drugs, and their effects are short lived. The only reported protein binding interactions with oral contraceptives involve anticonvulsants, not antibiotics [9,20].

Increased excretion of the contraceptive

Documented cases of increased urinary or fecal excretion of oral contraceptives by concomitant antibiotic use, including that caused by antibiotic-induced diarrhea, has not been substantiated in the literature.

Clinical studies evaluating the interaction

Although case reports should not be ignored and theoretically could indicate a rare interaction between antibiotics and oral contraceptives, a number of reviews have been published implying that the ability of commonly prescribed antibiotics to reduce the efficacy of oral contraceptives is an established, proven drug interaction [25–27]. An excerpt of such an article read, "The antibiotics that interfere with the ovulatory inhibiting effects of oral contraceptives are penicillin V potassium, amoxicillin, cephalexin, tetracycline and erythromycins" [27]. Unfortunately, these authors cited previously published case reports and not any controlled studies or pharmacokinetic data [28]. In 1991, the American Dental Association (ADA) Health Foundation Research Institute added "fuel to the fire" by publishing a statement that read "…Many antibiotics commonly used in dentistry interfere with the action of oral contraceptives, resulting in unexpected pregnancies" [29].

Many experts refer to the study published by Williams and Pulkinnen in 1971 as scientific proof of an interaction between antibiotics and oral contraceptives [30]. Although the authors reported reduced estrogen concentrations in pregnant patients taking ampicillin, this study did not evaluate the effect of ampicillin on blood levels of the estrogen or progestin component of oral contraceptives. Since then, a number of studies have looked directly at oral contraceptive blood levels in both the absence and presence of antibiotic treatment. All studies reached a similar conclusion. The concomitant

ingestion of ampicillin, tetracycline, doxycycline, metronidazole, erythromycin, clarithromycin, temafloxacin, or fluconazole did not reduce plasma levels of either the estrogen or progestin component of the oral contraceptive [21,24,31–36]. The results of one such study with the antibiotic doxycycline [36], a drug that is being widely employed in periodontal therapy, is illustrated in Fig. 3.

A second type of study addressing the interaction has analyzed unintended pregnancy rates as the outcome measure in oral contraceptive users who consumed antibiotics. These studies have appeared in the dermatology literature and are retrospective by nature. In a survey that evaluated pregnancy rates in 34 oral contraceptive users who were prescribed erythromycin, tetracycline, or minocycline, a pregnancy rate of 1.4% per year was calculated [37]. This pregnancy rate did not differ from the accepted normal failure rate of oral contraceptives. In a larger retrospective study of 356 patients with a history of combined antibiotic-oral contraceptive use and of 425 women taking oral contraceptives without antibiotic exposure, Helms et al reported a yearly pregnancy rate of 1.6% in the antibiotic group and 0.96% in the control group [4]. There was no significant difference

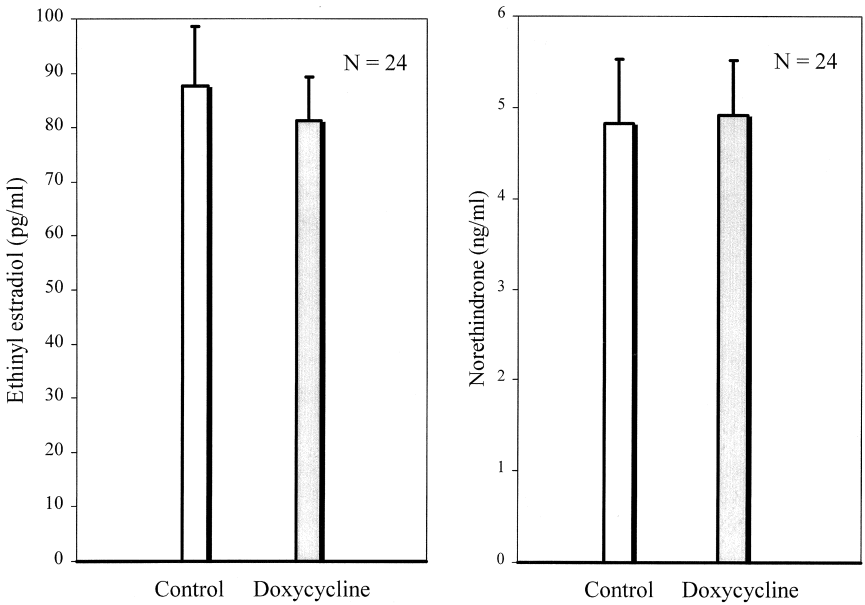

Fig. 3. Effects of doxycycline on blood levels of ethinyl estradiol and norethindrone. Women on a steady dose of Ortho-Novum® (35 ug ethinyl estradiol plus 1 mg norethindrone; Ortho-McNeil Pharmaceutical, Raritan, NJ) had serum concentrations of ethinyl estradiol and norethindrone measure on days 18, 19, and 20 of the menstrual cycle, both in the absence and presence of doxycycline therapy 100 mg twice daily. There were no significant reductions in serum concentrations (mean ± SE) of either hormonal constituent during antibiotic therapy ($p = 0.49$ for ethinyl estradiol concentrations and $p = 0.36$ for norethindrone concentrations, paired student t tests).

($P = 0.4$) in pregnancy rates between the antibiotic and control groups, and both groups had pregnancy rates blow the 3% failure rate typically found in the United States.

Legal actions and opinions

Reports of at least two successful litigations (settled out of court) involving unintended pregnancies in oral contraceptive users prescribed antibiotics by dentists who failed to warn the patients of the possibility of reduced oral contraceptive efficacy continues to be emphasized by dental/legal experts [38]. Unfortunately, these legal proceedings cannot be researched or even substantiated. In the one published case where a plaintiff and her husband sued an army-based oral surgeon and gynecologist for malpractice and "wrongful life" for not warning her of a potential antibiotic/oral contraceptive interaction and the unintended pregnancy that allegedly occurred either during or shortly after she was prescribed penicillin V, the health professionals were exonerated [39]. In summarizing these legal proceedings, the patient and her husband lost the case for the following reasons:

(1) Her experts were unable to cite a single published scientific study that statistically demonstrated an association between penicillin use and oral contraceptive failure
(2) The scientific studies that her experts did cite all demonstrated a lack of interaction between commonly employed antibiotics and oral contraceptives
(3) All review articles cited by her experts supporting the interaction were not evidence-based
(4) Under California law, rare risks of drug therapy do not have to be discussed (ie, the risk of contraceptive failure during antibiotic therapy would have to be at least double the normal failure rate for the necessity of informed discussion)
(5) Her experts were unable to prove that she became pregnant either during or shortly after she was taking penicillin.

Summary

With the exception of rifampin-like drugs, there is a lack of scientific evidence supporting the ability of commonly prescribed antibiotics, including all those routinely employed in outpatient dentistry, to either reduce blood levels and/or the effectiveness of oral contraceptives. To date, all clinical trials studying the effects of concomitant antibiotic therapy (with the exception of rifampin and rifabutin) have failed to demonstrate an interaction. Like all drugs, oral contraceptives are not 100% effective with the failure rate in the typical United States population reported to be as high as 3%. It is thus

possible that the case reports of unintended pregnancies during antibiotic therapy may simply represent the normal failure rate of these drugs. Considering that both drug classes are prescribed frequently to women of childbearing potential, one would expect a much higher rate of oral contraceptive failure in this group of patients if a true drug:drug interaction existed. On the other hand, if the interaction does exist but is a relatively rare event, occurring in, say, 1 in 5000 women, clinical studies such as those described in this article would not detect the interaction. The pharmacokinetic studies of simultaneous antibiotic and oral contraceptive ingestion, and the retrospective studies of pregnancy rates among oral contraceptive users exposed to antibiotics, all suffer from one potential common weakness, ie, their relatively small sample size. Sample sizes in the pharmacokinetic trials ranged from 7 to 24 participants, whereas the largest retrospective study of pregnancy rates still evaluated less than 800 total contraceptive users. Still, the incidence of such a rare interaction would not differ from the accepted normal failure rate of oral contraceptive therapy.

The medico-legal ramifications of what looks like at best a rare interaction remains somewhat "murky." On one hand, we have medico-legal experts advising the profession to exercise caution and warn all oral contraceptive users of a potential reduction in efficacy during antibiotic therapy. These opinions are not evidence-based and rely heavily on one or two legal proceedings that cannot even be substantiated. On the other hand, there is one recently published legal proceeding in which the outcome was in favor of the oral surgeon. There is clearly a need for additional scientific research in oral contraceptive users that incorporates larger sample sizes, different time courses (prophylactic use versus standard 7–10 day use versus extended use), and different delivery systems (systemic administration versus local-controlled delivery) of antibiotic therapy. Though experts on this topic still recommend informing oral contraceptive users of the potential for a rare interaction, and for clinicians to advise them to employ additional barrier techniques of birth control during antibiotic therapy and for at least 1 week beyond the last dose [40], it is hoped that a set of guidelines regarding this controversy will eventually be published that is evidence-based, and not solely the results of anecdotal reports, expert opinions, and legal proceedings.

References

[1] Miller DM, Helms SE, Brodell RT. A practical approach to antibiotic treatment in women taking oral contraceptives. J Am Acad Dermatol 1994;30:1008–111.
[2] Goldfien A. The gonadal hormones and inhibitors. In: Katzung BG, editor. Basic and clinical pharmacology. 7th edition. Stamford: Appleton & Lange; 1998. p. 989–97.
[3] Weisberg E. Interactions between oral contraceptives and antifungal/antibacterials. Is contraceptive failure the result? Clin Pharmacokinet 1999;36(5):309–13.
[4] Helms SE, Bredle DL, Zajic J, et al. Oral contraceptive failure rates and oral antibiotics. J Am Acad Dermatol 1997;36:705–10.

[5] Sondheimer SJ. Update on oral contraceptive pills and postcoidal contraception. Curr Opin Obstet Gynecol 1992;4(4):502–5.
[6] Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. JAMA 2000;284(1):72–8.
[7] Reimers D, Jezek A. The simultaneous use of rifampicin and other antitubercular agents with oral contraceptives. Prax Pneumol 1971;25(5):255–62.
[8] Noche-Fink I, Breuer H, Reimers D. Effects of rifampicin on the menstrual cycle and on estrogen excretion in patients taking oral contraceptives. JAMA 1973;226(3):378.
[9] Szoka PR, Edgren RA. Drug interactions with oral contraceptives: compilation and analysis of an adverse experience report database. Fertil Steril 1988;29(5 suppl 2):31s–38s.
[10] Back DJ, Breckenridge AM, Crawford FE, et al. The effect of rifampicin on the pharmacokinetics of ethinyl estradiol in women. Contraception 1980;21(2):135–43.
[11] Back DJ, Breckenridge AM, Crawford FE, et al. The effect of rifampicin on norhisterone pharmacokinetics. Eur J Clin Pharmacol 1979;15:193–7.
[12] Barditch-Crovo P, Trapnell CB, Ette E, et al. The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive. Clin Pharmacol Ther 1999;65(4):428–38.
[13] Michaelets EL. Update: clinically significant cytochrome p450 drug interactions. Pharmacotherapy 1998;18(1):84–112.
[14] Dosseter J. Drug interaction with oral contraceptives. Br Med J 1975;4(5994):467–8.
[15] Bacon JF, Shenfield GM. Pregnancy attributable to interaction between tetracyclines and oral contraceptives. Br Med J 1980;280(6210):293.
[16] DeSano EA, Hurley SC. Possible interactions of antihistamines and antibiotics with oral contraceptive effectiveness. Fertil Steril 1980;37(6):853–4.
[17] Bainton R. Interaction between antibiotic therapy and contraceptive medication. Oral Surg 1986;61:453–5.
[18] Back DJ, Grimmer SF, Orme ML, et al. Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. Br J Clin Pharmacol 1988;25(5):527–32.
[19] Donley TG, Smith RF, Roy B. Reduced oral contraceptive effectiveness with concurrent antibiotic use: a protocol for prescribing antibiotics to women of childbearing age. Compend Contin Educ Dent 1990;9(6):392–6.
[20] Shenfield GM. Drug interactions with oral contraceptives. Med J Aust 1986;144:205–11.
[21] Back DJ, Breckenridge AM, MacIver M, et al. The effects of ampicillin on oral contraceptive steroids in women. Br J Clin Pharmac 1982;14:43–8.
[22] Back DJ, Breckenridge AM, Cross KJ, et al. An antibiotic interaction with ethinyl estradiol in the rat and rabbit. J Steroid Biochem 1982;16(3):407–13.
[23] Back DJ, Orme ML. Pharmacokinetics drug interaction with oral contraceptives. Clin Pharmacokin 1990;18(6):472–84.
[24] Orme ML, Back DJ. Interactions between oral contraceptive steroids and broad-spectrum antibiotics. Clin Exp Dermatol 1986;11(4):327–31.
[25] Fazio A. Oral contraceptive drug interactions: important considerations. South Med J 1991;84(8):997–1002.
[26] Pyle MA, Faddoul FF, Terezhalmy GT. Clinical implication of drugs taken by our patients. Dent Clin North Am 1993;37(1):73–90.
[27] Wynn RL. The top 50 drugs dispensed by pharmacies in 1996. Gen Dent 1997;45(5): 416–20.
[28] Hersh EV. Adverse drug interactions in dental practice: interactions involving antibiotics. J Am Dent Assoc 1999;130:236–51.
[29] ADA Health Foundation Research Institute, Department of Toxicology. Antibiotic interference with oral contraceptives. J Am Dent Assoc 1991;122(12):79.
[30] William K, Pulkkinen MO. Reduced maternal plasma and urinary estriol during ampicillin treatment. Am J Obstet Gynecol 1971;109(6):893–6.

[31] Back DJ, Tjia J, Martin C, et al. The interaction between clarithromycin and oral contraceptive steroids. J Pharm Med 1991;2(1):81–7.
[32] Back DJ, Tjia J, Martin C, et al. The lack of interaction between temafloxacin and combined oral contraceptive steroids. Contraception 1991;43(4):317–23.
[33] 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(6):643–52.
[34] Lazar JD, Wilner KD. Drug interactions with fluconazole. Rev Infect Dis 1990;12(suppl 3):S327–33.
[35] Murphy AA, Zacur HA, Charche P, et al. The effect of tetracycline on levels of oral contraceptives. Am J Obstet Gynecol 1991;164(1):28–33.
[36] Neely JL, Abate M, Swinker M, et al. The effect of doxycycline on serum levels of ethinyl estradiol, norethindrone, and endogenous progesterone. Obstet Gynecol 1991;77(3): 416–20.
[37] London BM, Lookingbill DP. Frequency of pregnancy in acne patients taking oral antibiotics and oral contraceptives. Arch Dermatol 1994;130:392–3.
[38] Zinman EJ. Legal considerations. In: Newman MG, van Winkelhoff AJ, editors. Antibiotics and antimicrobial use in dental practice. 2nd edition. Chicago: Quintessence Publishing Co, Inc; 2001. p. 257–72.
[39] California court denies wrongful birth claim. J Law Med Ethics 1996;24(3):273–4.
[40] Burroughs KE, Chambliss ML. Antibiotics and oral contraceptive failure. Arch Fam Med 2000;9(1):81–2.