

Patients Get New Rights to Appeal Insurance Decisions

BY MARY ELLEN SCHNEIDER

New federal regulations mandated by the Affordable Care Act will give patients new rights to appeal claims denials made by their health plans.

The rules will allow consumers in new health plans to appeal decisions both through their insurer's internal process and to an outside, independent entity. While most health plans already provide for an internal appeals process, not all offer an external review of plan decisions, according to the U.S. Department of Health and Human Services. The types of appeals processes often depend on individual state laws.

HHS officials estimate that in 2011 there will be about 31 million people in new employer plans and another 10 million people in new individual market plans who will be able to take advantage of these new appeals opportunities. By 2013, that number is expected to grow to 88 million people. The rules do not apply to grandfathered health plans.

Under the new rules, health plans that begin on or after Sept. 23, 2010, must have an external appeals process that allows consumers to appeal whenever the plan denies a claim for a covered service or rescinds coverage. The internal appeals process must also offer consumers detailed information about the grounds for their denial and information on how to file an appeal. The new rules aim to make internal appeals more objective by ensuring that the person considering the appeal does not have a conflict of interest. For example, the health plan is not allowed to offer financial incentives to employees based on the number of claims that are denied. Health plans will also have to provide an expedited appeals process.

The new federal appeals regulations also standardize rules for external appeals.

Currently, 44 states require health plans to have some type of external appeal but those processes vary greatly, according to HHS. Under the federal rules, health plans must provide clear information about external appeals and expedited access to the process. The decisions made through external appeals are binding under the new federal rules.

YAZ® (drospirenone and ethinyl estradiol) Tablets

6700401BS

Brief Summary of Prescribing Information, RX only

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES

INDICATIONS AND USAGE 1. YAZ is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive. 2. YAZ is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of YAZ for PMDD when used for more than three menstrual cycles has not been evaluated. YAZ has not been evaluated for the treatment of premenstrual syndrome (PMS). 3. YAZ is indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy. 4. YAZ is also indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy. 5. YAZ should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control. **CONTRAINDICATIONS** YAZ should not be used in women who have the following: • Renal insufficiency • Hepatic dysfunction • Adrenal Insufficiency • Thrombophlebitis or thromboembolic disorders • A past history of deep-vein thrombophlebitis or thromboembolic disorders • Cerebral-vascular or coronary-artery disease (current or history) • Valvular heart disease with thrombotic complications • Severe hypertension • Diabetes with vascular involvement • Headaches with focal neurological symptoms • Major surgery with prolonged immobilization • Known or suspected carcinoma of the breast • Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia • Undiagnosed abnormal genital bleeding • Oligospermia of pregnancy or jaundice with prior pill use • Known or suspected pregnancy • Liver tumor (benign or malignant) or active liver disease • Heavy smoking (≥ 15 cigarettes per day) and over age 35 • Hypersensitivity to any component of this product

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

YAZ contains 3 mg of the progestin drospirenone that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. YAZ should not be used in patients with conditions that predispose to hyperkalemia (i.e., renal insufficiency, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle. Medications that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDs. The use of oral contraceptives is associated with increased risks of several serious conditions, including thrombotic and thromboembolic disorders, myocardial infarction, stroke, hypertension, hyperlipidemia, morbid obesity, and diabetes. The relative risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemia, obesity and diabetes. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks. The information contained in this package insert is based principally on studies carried out in patients who used oral contraceptives with higher formulations of estrogen and progestin than those contained in YAZ. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined. Throughout this labeling, epidemiologic studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiologic methods. 1. **THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS a. Myocardial Infarction** An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30. Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their 30s and older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in women over the age of 35 who are current or former oral contraceptive users. The relative risk of stroke has been shown to be similar for oral contraceptives. Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemia, age and obesity. In particular, some progestogens are known to increase HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see section 9 in **WARNINGS**). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors. **b. Thromboembolism** An increased risk of thrombotic and thromboembolic diseases associated with the use of oral contraceptives is well established. Case-control studies have found a relative risk for users compared to nonusers to be 3 for the first episode of superficial thrombophlebitis, 4 to 11 for deep vein thrombophlebitis or pulmonary embolism, and 1.5 to 1.6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease is not related to length of use and disappears after pill use is stopped. A two- to four-fold increase in the relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of stroke has been shown to be two to four times that of women without such medical conditions. If feasible, oral contraceptives should be discontinued from at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, combined oral contraceptives should be started no earlier than four to six weeks after delivery and at that time only in women who elect not to breast feed. Several studies have investigated the relative risks of thromboembolism in women using a different drospirenone-containing COC (Yasmin, which contains 0.03 mg of ethinyl estradiol and 3 mg of drospirenone) compared to the risk in women using COCs with other progestins. Two prospective cohort studies evaluated the relative risk of venous and arterial thromboembolism and death, were initiated at the time of Yasmin approval.^{1,2} The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in Yasmin users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called third generation COC). The second prospective cohort study (Ingenuis) also showed a comparable risk of thromboembolism in Yasmin users compared to users of other COCs, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed Yasmin. Two additional epidemiological studies, one case-control study (van Hylkama Vlieg et al.)³ and one retrospective cohort study (Lidegaard et al.)⁴ suggested that the risk of venous thromboembolism occurring in Yasmin users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so-called third generation COCs). In the case-control study, however, the number of Yasmin cases was very small (1.2% of all cases) making the risk estimates unreliable. The relative risk for Yasmin users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include users who used the products for more than one year. The relative risk for Yasmin users was similar to users of Yasmin to that for users of other COC products. **2. Cerebrovascular diseases** Oral contraceptives have been shown to increase both the relative and attributable risks for cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor, for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes. In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for normotensive users and 2.6 for users with severe hypertension. The relative risk of stroke has been shown to be 2.0 for current or former oral contraceptive users and 1.8 for noncurrent users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women. Oral contraceptives also increase the risk for stroke in women with other underlying risk factors such as certain inherited or acquired thrombophilias, hyperlipidemia, and obesity. Women with migraine (particularly migraine with aura) who take combination oral contraceptives may be at an increased risk of stroke. **d. Dose-related risk of vascular disease from oral contraceptives** A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents in high doses. In addition, there is a decline in HDL with the use of low-dose formulations. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive. Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptant users of combination oral contraceptives should start on preparations containing the lowest estrogen content that is judged appropriate for the individual patient. **Persistence of risk of vascular disease** There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women aged 40 to 49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was only maintained in non-smoking women who had used oral contraceptives for five or more years. Risks of disease are related to excess risk of users of oral contraceptives. **3. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE** One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages. These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is below that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data from a retrospective cohort study of women who used oral contraceptives for 5 years or more. This study involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling. Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy nonsmoking women (even with the newer, low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, women of all ages who take oral contraceptives, should take the lowest possible dose formulation that is effective. **3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS** Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. Although the risk of breast cancer has increased among current and recent users of oral contraceptives, the increase in risk has been small (RR=1.24). This excess risk decreases over time after combination oral contraceptive discontinuation and by 10 years after cessation the increase risk disappears. The risk does not increase with duration of use and no consistent relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used oral contraceptives before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early oral contraceptive use is extremely small. Breast cancers diagnosed in current or previous COC users tend to be less clinically advanced than in never users. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormonally-sensitive tumor. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established. **4. HEPATIC NEOPLASIA** Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users. A risk that increases after four or more years of use. Rupture of a large, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users. **5. OCULAR LESIONS** There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. This may lead to partial or complete loss of vision. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision, proptosis or diplopia, papilledema, or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately. **6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY** Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion. (See **CONTRAINDICATIONS**). It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed dosing schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed. **7. GALLBLADDER DISEASE** Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk

may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens. 8. **CARBOHYDRATE AND LIPID METABOLIC EFFECTS** Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogen cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives. A small proportion of women will have persistent hyperglycemia while on the pill. As discussed earlier (see **WARNINGS**, 1a, and 1c), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users. 9. **ELEVATED BLOOD PRESSURE** Women with severe hypertension should not be started on hormonal contraceptives (see **CONTRAINDICATIONS**). An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens. Women with a history of hypertension or hypertension-related disease, or renal disease should be encouraged to use another method of birth control. If women with hypertension elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives and there is no difference in the occurrence of hypertension among ever- and never-users. **10. HEADACHE** The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause. **11. BLEEDING URREGULARITIES** Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out. Some women may experience more post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent. **PRECAUTIONS 1. GENERAL** Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases. **2. PHYSICAL EXAMINATION AND FOLLOW-UP** A periodic personal and family medical history and complete physical examination are appropriate for all women, including women using oral contraceptives. Some progestogens may slightly increase LDL levels and may increase the risk of hyperlipidemia, therefore difficult. (See **WARNINGS**, 1a). In patients with a clinical condition that requires estrogen-containing preparations, the physician should be aware of the possibility of significant elevations of plasma triglycerides leading to pancreatitis. **4. LIVER FUNCTION** If jaundice develops in any woman receiving oral contraceptives, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function. **5. FLUID RETENTION** Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. **6. EMOTIONAL DISORDERS** Women with a history of depression should be carefully observed and the drug discontinued if depression recurs or is severe. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. **7. CONTACT LENSES** Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist. **8. DRUG INTERACTIONS** Effects of Other Drugs on Combined Hormonal Contraceptives Rifampin: Metabolism of ethinyl estradiol and some progestins (e.g., norethindrone) is increased by rifampin. A reduction in contraceptive effectiveness and an increase in menstrual irregularities have been associated with concomitant use of rifampin. **Minoxycline**: Minoxycline-related changes in estradiol, progesterone, FSH and LH plasma levels, breakthrough bleeding, and contraceptive failure have been reported. **Anticoagulants**: Anticoagulant therapy, such as warfarin, phenindione, and carbamazepine have been shown to increase the metabolism of ethinyl estradiol and/or some progestins, which could result in a reduction of contraceptive effectiveness. **Antibiotics**: Pregnancy while taking combined hormonal contraceptives has been reported when the combined hormonal contraceptives were administered with antimicrobials such as ampicillin, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effects of antibiotics (other than rifampin—see above) on plasma concentrations of synthetic steroids. See also separate discussion on minocycline (above). **Mitomycin**: Coadministration of mitomycin and an oral contraceptive increased AUC values for ethinyl estradiol by approximately 30% and drospirenone by approximately 20%, respectively. **St John's Wort**: St John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of oral contraceptives and emergency contraceptive pills. This may also result in breakthrough bleeding. **Other**: Ascorbic acid and acetaminophen may increase plasma concentrations of some synthetic estrogens, possibly by inhibition of conjugation. **Effects of Drospirenone on Other Drugs** **Metabolic Interactions** Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies. (See **Metabolic Interactions** in full package insert.) *In vitro* studies: DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women (including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype) the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (140 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. Furthermore, no significant effect of DRSP on systemic clearance of the CYP3A4 product omeprazole was found. These results demonstrate that DRSP did not inhibit CYP1A2, CYP2C9, CYP2C19 and CYP3A4 *in vivo*. Two additional clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4 were each performed in 24 healthy postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day. **Interactions with Drugs that Have the Potential to Increase Serum Potassium** There is a potential for an increase in serum potassium in women taking YAZ with other drugs (see **BOLD WARNING**). Of note, occasional or chronic use of NSAID medication was not restricted in any of the clinical trials with YAZ. A drug-drug interaction study with 3 mg DRSP/0.03 mg EE and 3 mg DRSP/0.03 mg EE versus placebo was conducted in 24 healthy women. In the 24-month oral contraceptive study (10 mg twice daily, Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/EE treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium Cmax and AUC in the DRSP/EE group to those in the placebo group were 0.855 (90% CI: 0.914, 0.999) and 1.01 (90% CI: 0.944, 1.08), respectively. No patient in either the DRSP/EE or placebo group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L). **Effects of Combined Hormonal Contraceptives on Other Drugs** Combined oral contraceptives containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance on temazepam, salicylic acid, morphine, and clofibrate acid have been noted when these drugs were administered with oral contraceptives. **3. INTERACTIONS WITH LABORATORY TESTS** Certain endocrine- and liver-function tests and blood components may be affected by oral contraceptives: a. Increased prothrombin and fibrinogen levels; b. Increased triglyceride levels; c. Increased hemoglobin and hematocrit; d. Increased serum cholesterol; e. Increased binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 concentration is unaltered. c. Other binding proteins may be elevated in serum. f. Sex hormone-binding globulin are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged. g. Triglycerides may be increased. h. Glucose tolerance may be decreased. g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after oral contraceptive use. **10. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS** Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. Although the risk of breast cancer has increased among current and recent users of oral contraceptives, the increase in risk has been small (RR=1.24). This excess risk decreases over time after combination oral contraceptive discontinuation and by 10 years after cessation the increase risk disappears. The risk does not increase with duration of use and no consistent relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used oral contraceptives before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early oral contraceptive use is extremely small. Breast cancers diagnosed in current or previous COC users tend to be less clinically advanced than in never users. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormonally-sensitive tumor. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. 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