Neurology®

March 28, 2006; 66 (66 suppl 3) ARTICLES

An overview of oral contraceptives

Mechanism of action and clinical use

Cheryl A. Frye

First published March 27, 2006, DOI: https://doi.org/10.1212/WNL.66.66_suppl_3.S29

Abstract

Hormonal contraception is available in oral contraceptive pills and in newer formulations, including the transdermal patch, the vaginal ring, subcutaneous implants, and IM injections. Prevention of pregnancy is achieved by inhibiting ovulation, fertilization, and/or implantation of an egg. Hormonal contraception provides effective, tolerable, and reversible prevention of pregnancy. Efficacy and safety profiles are similar for different formulations and administration routes. Lowest expected failure (i.e., method failure) rates for hormonal

contraceptives, regardless of formulation, are <2%. Typical failure rates for oral formulations range from <3% to 5% due to failures in compliance. The most commonly reported adverse effects are weight gain, nausea, variations in menstrual flow, breast changes such as tenderness, discomfort, or swelling, depression or mood disturbances, decreased sexual desire or response, and acne. Rare but serious potential effects include cardiovascular diseases, such as stroke, and an increased risk for breast cancer, liver tumors, and gallbladder disease. Hormonal contraceptive use should be avoided in women at risk for blood clots, by heavy smokers, and in women with breast or other cancers. Use of hormonal contraception in adolescents requires special consideration, in part because of decreased compliance.

Oral contraceptives (OCs) are the most commonly used method of birth control in the United States.[1] Worldwide, more than 100 million women use OCs,[2] which offer ease of use, reliability, and tolerability. Newer forms of hormonal contraception, including transdermal patches, vaginal rings, implants, and IM injections, may increase convenience and compliance.

Because the concomitant use of hormonal contraceptives and cytochrome P-450 enzyme-inducing antiepileptic drugs (AEDs) decreases the efficacy of the contraceptives,[3] the use of such contraceptives poses special concerns for patients with epilepsy. This article reviews the mechanism of action, efficacy, and tolerability of common hormonal contraceptives. For a discussion of the direct effects of hormonal contraception on epilepsy, see "Antiepileptic Drugs and Hormonal Contraceptives in Adolescent Women With Epilepsy" by Mary L. Zupanc, MD (on page **S37**).

Hormonal contraceptives in common use.

Hormonal contraceptives can be categorized on the basis of their hormonal components (table 1) and the relative content of those components (table 2).

Table 1 *Hormonal contraceptives in common use*[4]

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Table 2 *Relative progestin-estrogen content of hormonal contraceptive agents*

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Combination and estrogen-only contraceptives.

Combination hormonal contraceptives include both progestin and estrogen components and are most commonly used for OC regimens. Combination contraceptives deliver constant levels of both hormones (monophasic combinations) or increasing concentrations of progestin and/or estrogen (biphasic or triphasic combinations) throughout the monthly cycle. Biphasic combinations employ two different doses of hormones divided into two phases during the cycle, whereas triphasics employ three doses in three phases during the cycle. Biphasic combinations deliver a low dose of estrogen with an escalating concentration of progestin but are uncommonly used. In triphasic combinations, the overall doses of both hormones are relatively low, and estrogen levels may increase at midcycle or remain constant while progestin levels increase.[4]

Newer contraceptive formulations using alternative administration routes offer patients increased convenience and promote compliance, with minimal reliance on patient initiative. Weekly transdermal patches and 3-week or 3-month vaginal rings release either a sustained low-dose combination of estrogen and progestin or estrogen alone and require less frequent administration than OCs.[5–7] Recently introduced extended-cycle regimens (e.g., Seasonale) employ the hormonal components of traditional hormonal contraceptives. In these regimens, active pills are continued for 84 days rather than 21 days, so that menstruation occurs once every 3 months rather than monthly. Unintended pregnancy is most likely to occur if missed doses are in close chronologic proximity to the inactive doses. Because of this likelihood, a reduction in inactive doses from 13 times per year (conventional hormonal contraceptives) to four times per year (extended-cycle regimens) may decrease the failure rate.[8]

Progestin-only contraceptives.

Because many serious adverse effects of hormonal contraceptives are associated with high doses of estrogen, lower-dose formulations and progestin-only preparations were designed to offer increased safety.[1,4] Progestin-only hormonal contraceptives are slightly less effective than combination pills and are uncommon in oral formulations.[4] However, implants such as Norplant (not available in the United States), which can last as long as 5 years, and IM injections, such as Depo-Provera, which are administered every 3 months, are available exclusively as progestin-only formulations.

Mechanism of action of hormonal contraception.

Estrogen and progestin are active components of hormonal contraception (table 3). Their primary mechanism of action is believed to be prevention of ovulation. Estrogen prevents release of follicle-stimulating hormone (FSH),[4] thus inhibiting ovarian activity and preventing development of an ovum.[1] Progestin has a variety of effects, including thickening of cervical mucus, decreased tubal mobility, changes in the endometrium, and prevention of ovulation. Thickening of cervical mucus hinders sperm penetration, whereas decreased tubal mobility inhibits ovum transport and fertilization and may affect sperm migration and activity. Finally, changes in the endometrium may affect survival of a blastocyst within the uterus or prevent implantation.[4,40,41]

Table 3 *Effects of estrogen and progestin components in hormonal contraception*[4,40,72]

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Emergency contraception.

Hormonal contraception is also used as emergency contraception to prevent pregnancy after unprotected intercourse or contraceptive failure. Treatment consists of two doses of hormone given 12 hours apart and is most effective when administered within 72 hours of unprotected sex. Two regimens are generally accepted: combination estrogen/progestin, known as the Yuzpe regimen (Preven), or progestin only (Plan B).[1,4,42] Both regimens may be accomplished using traditional OC pills given at increased doses.[1,42]

The mechanism of action of emergency contraception is not clearly understood, but evidence suggests that its activities parallel those of hormonal contraception. The primary activity of emergency contraception is believed to be prevention of ovulation. However, it is likely that other effects contribute to the prevention of pregnancy. The hormonal components of emergency contraception act similarly to continuous hormonal contraception, interfering with ovum transport, fertilization, and implantation, and inhibiting sperm mobility by thickening cervical mucus.[4,42] Importantly, evidence indicates that emergency contraception cannot interrupt an established pregnancy, ensuring the emergency contraception method's fundamental difference from medical abortion.[42] There is no evidence that hormonal emergency contraception damages the fetus either in an established pregnancy or in the case of treatment failure.[1,42,43]

Clinical use of hormonal contraceptives.

Efficacy.

Hormonal contraception offers highly effective, reversible prevention of pregnancy, regardless of formulation (table 4). Efficacy is reported as failure rate during 1 year of use. The lowest expected failure rate approximates ideal results with no human error. The typical expected failure rate reflects a more realistic estimate of failure. The lowest expected failure rate of hormonal contraception, regardless of formulation, is <2%, whereas the typical failure rate of oral formulations is <3% to 5%. Although lowest expected failure rates of combination OCs and progestin-only OCs differ slightly, the typical failure rates of all OCs are equivalent. Notably, the typical failure rates of OCs are substantially higher than the lowest expected failure rates, whereas the typical failure rates of implants and IM injections are identical to the lowest expected failure rates, an effect that is considered to be due to increased compliance.[1,4,44]

Table 4 *Efficacy of hormonal contraceptives*[4,44,73]

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Other health benefits of hormonal contraceptives.

Hormonal contraception confers several health benefits beyond contraception itself. The two most consistently demonstrated benefits are a decrease in the incidence of benign breast disease (both fibrocystic and fibroadenomatous) and a reduction in retention cysts of the ovary. Other health benefits include decreased iron-deficiency anemia (due to lighter menstrual flow) and potentially decreased incidences of pelvic inflammatory disease, ectopic pregnancy, rheumatoid arthritis, endometrial cancer, and ovarian cancer. Considered overall, the combined health benefits of hormonal contraceptive use may prevent up to 50,000 hospitalizations yearly.[1,4,45] Women using hormonal contraception may also experience less cramping during menstruation and decreased premenstrual tension. Acne may decrease with some formulations of estrogen-containing hormonal contraceptives [such as Ortho Tri-Cyclen (norgestimate and ethinyl estradiol)].[4,30,46] In addition, long-term users of hormonal contraceptives may maintain a higher bone mineral density.[4]

Safety.

Hormonal contraception is generally well tolerated, and serious adverse events are rare (table 5). The most common adverse effect of hormonal contraception is nausea, which usually resolves within 3 months and may be reduced with lower-dose estrogen (20 μg).

Other common adverse effects include variations in menstrual flow and breakthrough bleeding, breast changes (tenderness, discomfort, or swelling), depression and other mood disturbances, decreased desire or sexual response, dermatologic effects including acne, and gum inflammation.[1,4]

Table 5 *Adverse effects of hormonal contraceptives*[1,4,40,48]

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Rare but serious potential risks and long-term toxicities of hormonal contraception have long been understood. The most serious adverse events associated with hormonal contraception are cardiovascular diseases, such as hypertension, heart attack, stroke, pulmonary embolism, and clotting disorders. Less than 5% of women using hormonal contraception develop hypertension, which may increase their risk for heart attack and stroke. Overall, hormonal contraceptive use is associated with a 1/66,700 risk for death, mainly due to cardiovascular diseases.[4,47] Other serious effects include an increased risk for breast cancer, gallbladder disease, and liver tumors.[4,48,49] Severe headache is rare and may be an early warning of stroke. These risks increase with age and a history of smoking.[1,47] Hormonal contraceptive use may also be associated with the development of some forms of cervical cancer. Therefore, yearly Pap smears are strongly recommended for all women who use this form of birth control.[4]

The risk for thrombotic events may be increased with some formulations of hormonal contraception. Agencies outside the United States have warned against the use of third-generation oral contraceptives, which contain a new form of progestin (desogestrel), because of a possible increase in the risk for serious nonfatal blood clots. The strength of the evidence for this effect is unclear.[50] To date, it has not been recommended that women in the United States discontinue use of desogestrel-containing regimens.[51]

Formulations of hormonal contraceptives, such as IM injections, transdermal patches, and implants, have tolerability comparable to that of traditional OCs. The primary reasons for discontinuation are weight gain, headaches, depression or mood changes, acne, breast pain or tenderness, and bleeding irregularities.[52–54] Weight gain and acne or skin problems may increase with duration of use and may be more common with implants than with OCs.[52,53] Nevertheless, because of their ease of use, implants have a significantly higher rate of continued use at 1 year compared with OCs.[53]

Emergency contraception: efficacy and safety.

Although the efficacy of emergency contraception is difficult to quantify, it appears to be a very effective intervention, particularly when used shortly after unprotected intercourse. Efficacy measures are based on hypothetical estimates of numbers of pregnancies that would have occurred in the absence of intervention.[55] The presumed percentage of pregnancies prevented varies widely across studies. However, a rate of approximately 75% is generally accepted.[4,42,43,55]

Emergency contraceptive treatment is generally tolerable, although nausea and vomiting are common (up to 50% and 20%, respectively), and there are no known long-term effects because of the short duration of treatment. Other adverse effects include irregular bleeding, dizziness, fatigue, headache, breast tenderness, and lower abdominal pain, which resolve within a few days. Nausea and vomiting are minimized with progestin-only emergency contraception.[1,4,42,43,47] Although emergency hormonal contraception is an effective and tolerable intervention, by comparison, emergency contraception using an intrauterine device (IUD) offers greatly improved efficacy, with an estimated failure rate of 0.1% compared with 0.6% to 1.8% with hormonal emergency contraception.[55,56]

Hormonal contraceptives in special populations.

Careful consideration of the benefits and risks of hormonal contraceptives is warranted in all women. Specifically, hormonal contraceptives are contraindicated in women with any condition that may cause excess clotting or in those who have a history of stroke, heart disease, liver disease, breast cancer, or hypertension. Because of the increased risk for adverse effects, women who are aged 35 years and smoke, women aged 40 years with another risk factor, and all women aged 50 years should consider alternate forms of contraception (table 6).[1,4]

Table 6 *Contraindications to hormonal therapy and other considerations*[1,4]

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Concurrent use of certain medications, including certain antibiotics and P-450 enzyme-inducing AEDs, decreases the effectiveness of hormonal contraception. Hormonal contraception may also alter the activity of other medications, including, but not limited to,

oral anticoagulants, antidepressants, β-blockers, and corticosteroids. Careful medical supervision is required with concurrent use of these medications and hormonal contraception.[1,4] (See page S37 for a full discussion of hormonal contraception and AED use.)

Special considerations with hormonal contraceptive use in adolescents.

The need for safe and effective contraception in adolescents is clear. Sexual activity is common among adolescents, with more than 40% of female high school students reporting that they have had sex.[57] Prevention of pregnancy in sexually active adolescents is not the only concern. Addressing the medical needs of sexually active adolescents should focus on both effective contraception and the prevention of sexually transmitted disease.[58] Selection of a contraceptive method in adolescents should include careful screening to probe for potential noncompliance and to explore possible patient apprehension about family and friends inadvertently discovering their contraceptive use.[58]

The primary concern with use of hormonal contraception in the adolescent population is poor compliance. Studies show that adolescents are less compliant with OC pills than their older counterparts,[59–61] putting adolescents at increased risk for unintended pregnancy. Compliance is affected by various factors, including attitudes toward sexuality, socioeconomic and environmental factors, access to sex education, confidentiality, self-esteem, and perception of contraceptive-related side effects.[54,61] Adolescents using OCs should be followed closely with an office visit after 1 month's use to verify patient compliance.[58] Newer options—including SC implants, transdermal patches, vaginal rings, and IM injections—may help ensure continuity of patient use. However, parental consent may be required in some states. Access to hormonal contraceptives and follow-up care may also be a limiting factor in adolescents' selection of these methods.

Although the primary issue in choosing a contraceptive method for adolescents is ensuring consistent level of compliance, there are other physiologic issues that must be recognized. In managing adolescent patients, it is essential to encourage their adequate dietary intake because certain nutritional requirements (e.g., vitamins C, B_2, B_{12}, B_6, and folic acid) are increased during the use of hormonal contraceptives owing to metabolic changes that occur within the first few months.[1] Most affected by these increases in nutritional needs are adolescents, low-income women, and those recovering from illness, surgery, or childbirth. After the first 6 months of therapy, a comprehensive physical examination with complete blood counts may be appropriate in women with suspected deficiencies. In addition, women

using hormonal contraception may develop impaired glucose tolerance. Patients should be counseled to maintain a healthful diet, reduce sugar intake, and take vitamin supplements. Vitamin C should be limited to <1,000 mg/day because high levels of vitamin C increase the serum concentration of estrogen in hormonal contraception.[4]

Some evidence suggests that risk for toxicity due to long-term hormonal contraceptive use is a concern in younger patients. Recent data indicate that the correlation between hormonal contraceptive use and breast cancer is strongest among younger women. Those who begin use of hormonal contraception before age 20 and continue this regimen for more than 4 years have an increased risk for development of breast cancer before 36 years of age. A trend toward increased risk for breast cancer is also indicated among women who begin hormonal contraceptive use early in their reproductive life (≤5 years after menarche).[62]

Finally, the risk for sexually transmitted disease is an important consideration for adolescents using hormonal contraception. Such contraception provides no protection against sexually transmitted disease, a fact that is particularly relevant if multiple sexual partners are involved. Adolescents frequently regard contraceptive methods primarily as means to prevent pregnancy rather than as safeguards against sexually transmitted disease.[63–65] Therefore, patients may not take appropriate measures to prevent disease, such as using condoms, if they feel that hormonal contraception alone is adequate. Several studies suggest that concomitant use of condoms is frequently poor or inconsistent among women taking hormonal contraceptives.[63–67]

Summary.

Today, women have more options for hormonal contraception than ever before. Multiple formulations of combination OC pills and newer administration methods, including the transdermal patch, vaginal ring, SC implants, and IM injections, are all in common use. Although prevention of pregnancy with hormonal contraception is primarily achieved through inhibition of ovulation (primarily due to the effects of estrogen), changes in cervical mucus and the endometrium, as well as other progestin effects, may also impede fertilization and implantation of an egg.[1,40,41]

Hormonal contraception provides effective, tolerable, and reversible prevention of pregnancy. The lowest expected failure rates, reflecting ideal conditions, are similar for different formulations and administration routes (0.1% to 1.6%). Typical failure rates, however, are higher for OC pills (2% to 5%) than for implants and injections because these latter administration methods are usually associated with higher compliance.[1,4,44] Safety profiles are also similar for different formulations. The most commonly reported adverse effects are weight gain, nausea, variations in menstrual flow, breast changes, depression or mood disturbances, decreased sexual desire or response, and acne. Serious potential adverse effects include cardiovascular diseases, such as stroke, and an increased risk for breast cancer, liver tumors, and gallbladder disease.[4,40,48,49]

Use of hormonal contraception in adolescents requires special consideration. Adolescents are less compliant with OC pills compared with adults.[59–61] In addition, adolescents may have limited access to hormonal contraceptives and follow-up care. Maintaining adequate nutrition and protecting against sexually transmitted disease by concomitant condom use are of particular concern in treating adolescents.

After four decades of clinical use, hormonal contraception remains a mainstay in pregnancy prevention. Worldwide, more than 100 million women rely on hormonal contraception,[2] which is among the most effective methods of reversible contraception, demonstrating typical failure rates comparable to those of IUD use and far superior to those of barrier methods.[44] In addition, hormonal contraception confers several health benefits, including decreased risk for benign breast disease, retention cysts in the ovary, iron-deficiency anemia, and endometrial and ovarian cancers.[1,4,45] Use of hormonal contraception may also decrease symptoms related to menstruation, including cramping and premenstrual tension.[1,4,46] Overall, hormonal contraception regimens, including oral contraception and other formulations, offer an effective, tolerable, and reversible option for prevention of pregnancy.

Footnotes

Publication of this supplement was supported by an educational grant from UCB Pharma Inc. The sponsor has provided the author with an honorarium for her participation in this project.

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