Hormonal contraception: recent advances and controversies

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This Educational Bulletin outlines delivery systems and contraceptive formulations, summarizes advances in emergency contraception and reviews the effects of hormonal contraception on cancer risks, cardiovascular disease, and bone. (Fertil Steril® 2008;90:S103–13. ©2008 by American Society for Reproductive Medicine.)

The first hormonal contraceptive, Enovid™ (150 μg of mestranol and 9.85 mg of norethynodrel; G.D. Searle, Skokie, IL), was approved by the U.S. Food and Drug Administration (FDA) for use in the United States in 1960. Oral contraceptives (OCs) are now the most widely used reversible form of hormonal contraception in the United States. A wide variety of hormonal contraceptives are available. Their mechanisms of action include inhibition of ovulation, alteration in cervical mucus, and/or modification of the endometrium, thus preventing implantation.

In addition to the contraceptive benefits, many other health benefits have been realized with hormonal contraception, including reduction of the risk of endometrial and ovarian cancers, control of menstrual bleeding, and relief from cyclic pelvic pain. In the evolution of hormonal contraception to its current form, modifications have been made in an effort to decrease side effects and improve effectiveness and compliance and to extend the time on active pills beyond 21 days. The first change was a decrease in the dose of estrogen and progestin, which led to the low-dose formulations used today (1). Subsequently, new progestins were developed to decrease androgenic side effects. More recently, alternative delivery systems have been introduced in an effort to improve tolerability, compliance, and convenience; these delivery systems include transdermal, vaginal, implantable, and injectable systems.

This bulletin will outline new delivery systems and contraceptive formulations, summarize recent advances in emergency contraception, and review the effects of hormonal contraception on cancer risks, cardiovascular disease, and bone health.

INJECTABLE PROGESTIN CONTRACEPTION

In December 2004, the FDA approved depo-subQ Provera 104™ (Pharmacia and Upjohn/Pfizer, New York, NY) for contraceptive use. The product contains 104 mg of medroxyprogesterone acetate in a pre-filled syringe with a 0.65 mL volume. It is administered subcutaneously every 12 to 14 weeks. The product contains 104 mg of medroxyprogesterone acetate in a pre-filled syringe with a 0.65 mL volume. It is administered subcutaneously every 12 to 14 days. The first change was a decrease in the dose of estrogen and progestin, which led to the low-dose formulations used today (1). Subsequently, new progestins were developed to decrease androgenic side effects. More recently, alternative delivery systems have been introduced in an effort to increase androgenic side effects. More recently, alternative delivery systems have been introduced in an effort to improve tolerability, compliance, and convenience; these delivery systems include transdermal, vaginal, implantable, and injectable systems.

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TRANSDERMAL HORMONAL CONTRACEPTION

The transdermal combined estrogen/progestin contraceptive patch (Ortho Evra™/Evra™; Ortho Women’s Health & Urology/Ortho-McNeil-Janssen Pharmaceuticals, Raritan, NJ) was approved by the FDA for use in the United States in 2002. The patch is 20 cm² (4 × 5 cm) and delivers 20 μg/day of ethinyl estradiol (EE) and 150 μg/day of norelgestromin (a biologically active metabolite of norgestimate) (4). The dosing is one patch weekly for 3 consecutive weeks, followed by a patch-free week. The patch may be applied to the buttock, abdomen, upper outer arm, or upper torso excluding the breasts. Mean serum concentrations of hormone are not affected by heat, humidity, exercise, or cold-water immersion (4). The observed contraceptive failure was 0.7 per 100 woman-years (95% confidence interval [CI], 0.31–1.10) but was higher in women with body weight >90 kg (5). The transdermal contraceptive is well tolerated and has a side-effect profile similar to OCs (6).

An open-label randomized study comparing the pharmacokinetics of EE showed that mean serum EE levels were 1.6 times higher with Ortho Evra than with a combination oral contraceptive pill containing 30 μg of EE (7). In November 2005, the FDA updated product labeling for Ortho Evra to warn providers and patients that the contraceptive patch exposes women to higher estrogen concentrations than most combination oral contraceptives. It is not known whether the contraceptive patch poses a higher risk for venous thromboembolic events (VTE) than oral contraceptives.

In 2008, the FDA approved labeling changes for the patch to include results from three epidemiologic studies evaluating insurance claims data demonstrating an elevated risk of VTE for patch users. Taken together, those data suggest that the
The risk of VTE for patch users may be up to two-fold greater than for women using OCs containing 30–35 μg of EE and norgestimate or levonorgestrel. The samples sizes among the three studies varied from 17 to 37 cases, and event rates ranged from approximately 11 to 42 cases per 100,000 women years. The risk of acute myocardial infarction and stroke have not been elevated in patch users compared with OC users, but events in both groups are too rare to provide a precise estimate of risk (8).

**CONTRACEPTIVE VAGINAL RING**

A combined estrogen/progestin contraceptive vaginal ring (CVR) (NuvaRing®; Organon USA, Roseland, NJ) was approved by the FDA for use in the United States in 2001. This contraceptive device consists of a flexible ring made of ethylene vinyl acetate copolymer with an outer ring diameter of 54 mm and a cross-sectional diameter of 4 mm. The vaginal ring releases approximately 120 μg of etonogestrel (a biologically active metabolite of desogestrel) and 15 μg of EE per day (9). The CVR is used for 3 weeks continuously followed by a 1-week, ring-free period to allow for regular menstrual bleeding. The advantage for the user is that the CVR is not fitted. It is inserted and removed by the user and may or may not be removed for coitus. The most common side effects reported include headache (6.6%), leukorrhea (5.3%), and vaginitis (5.0%) (10). The failure rate in one study was 0.65 per 100 woman-years (95% CI, 0.24–1.41) (10). An open-label, randomized study comparing the pharmacokinetics of EE showed that the mean serum EE levels with Ortho Evra are 3.4 times higher than with NuvaRing, and that the mean serum EE levels of combination oral contraceptive containing 30 μg of EE are 2.1 times higher than with NuvaRing (7). It is not known whether NuvaRing poses a lower risk for VTE than Ortho Evra or combination OCs.

**LEVONORGESTREL-RELEASING INTRAUTERINE DEVICE**

A levonorgestrel (LNG)-releasing intrauterine device (IUD) (Mirena®; Bayer HealthCare Pharmaceuticals, Wayne, NJ) was approved by the FDA for use in the United States in 2000. The LNG-IUD is T-shaped with a steroid reservoir containing 52 mg of levonorgestrel mixed with polydimethylsiloxane, which controls the release rate of hormone. The LNG-IUD is approved for 5 years. The LNG-IUD has a failure rate between 0 and 0.2 per 100 woman-years (11); the ectopic pregnancy rate is 0.02 per 100 woman years (12). Menstrual bleeding is decreased by 75% in LNG-IUD users and is attributed to the progestin-induced decidualization and suppression of the endometrium (13); 20% to 50% of users become amenorrheic within the first 2 years after insertion (14). After removal, there is rapid return to normal fecundability, with 1-year life-table pregnancy rates of 89 per 100 for women less than 30 years of age (15).

**IMPLANTABLE CONTRACEPTIVES**

Norplant® (Wyeth Pharmaceuticals Inc., Philadelphia, PA), the first implantable contraceptive device, was approved by the FDA for use in the United States in 1990 and was withdrawn from the market in 2002 due to complications associated with removal. This device contained 216 mg of levonorgestrel in six implantable rods to be removed after 5 years. Newer developments in implantable contraception are focusing on fewer implant and less androgenic progestins. Norplant® II (Jadelle®; Bayer Schering Pharma Oy, Turku, Finland) has been approved by the FDA but is not yet marketed in the United States. This system contains two rods, 4 cm in length, with a total dose of 150 mg of levonorgestrel for 3 years. The failure rate is 0.8 to 1.0 per 100 woman-years (16, 17).

In July 2006, the FDA approved a newer single-rod, nonbiodegradable implant system (Implanon™; Organon USA) containing the progestin etonogestrel (a desogestrel metabolite). The carrier polymer, ethylene vinyl acetate, is more stable than the silastic material used in Norplant. Implanon has been used widely throughout Europe, Australia, and Indonesia since 1998. It is implanted subdermally and results in serum progestin levels that inhibit ovulation and provide contraception for up to 3 years. There is a very low failure rate (<1 per 100 women-years), and ovulation resumes within 3 weeks of removal in more than 90% of women. Implanon is associated with irregular bleeding patterns. Specifically, up to 36% of women enrolled in clinical trials discontinued the method because of irregular bleeding or other progestin side effects (18). Implanon should be implanted between days 1 to 5 of a natural menstrual cycle or during the hormone-free week in women using OCs.

**ORAL CONTRACEPTIVES**

Oral contraceptive agents have been modified over time to limit estrogen and progestin dosage and decrease side effects. It has been established that progestin combinations with low-dose estrogens (30–35 μg of EE) are effective with limited side effects. Lower dose estrogens (20 μg of EE) and newer progestins subsequently have been introduced.

**Progestins**

The original progestins used in hormonal contraceptives were all derived from ethisterone, an orally active testosterone derivative. Removal of the carbon at the C-19 position confers progestational activity, with some residual androgenic activity (19). These 19-nortestosterone progestins are referred to as estranes, and include norethindrone, norethynodrel, norethindrone acetate, ethynodiol diacetate, and norethindrone enanthate. More simply, they belong to the norethindrone (norethisterone) family of progestins. The gonane family of progestins are 19-nortestosterone progestins structurally related to levonorgestrel, and they include levonorgestrel, norgestimate, desogestrel, and gestodene (not available in the United States).

The newer progestins of the levonorgestrel family (norgestimate, desogestrel, and gestodene) were designed to minimize androgenic side effects such as acne, hirsutism,
nausea, and lipid changes while increasing progestational effects (19). Among the progestins available in the United States, norgestimate has the greatest progestational effect, and levonorgestrel is the most androgenic (19). The newest progestin, drospirenone, is not a 19-nortestosterone derivative. The pharmacologic differences in progestins have not been reflected in clinical outcomes.

Drospirenone is an analog of the aldosterone antagonist spironolactone that exhibits both progestational and antian- drogenic activity (20). The 3-mg dose of drospirenone in OCs is approximately equivalent to 25 mg of spironolactone.

**Oral Contraceptives Containing Less Than 30 μg Ethinyl Estradiol**

Low-dose OCs with 20 μg of EE were initially marketed for use in perimenopausal women. However, these low-dose preparations have been shown to be effective contraceptive agents in women of reproductive age, with reported pregnancy rates ranging between 0.07 and 2.10 pregnancies per 100 woman-years of treatment (21). When compared with a 35-μg EE OC, the 20-μg EE OC has comparable cycle control and reduced symptoms of bloating and breast tenderness (22). There is no evidence, however, that OCs containing 20 μg of EE have a better safety profile than OCs containing 30 or 35 μg of EE. Similarly, multiphasic OC preparations have not been shown to be safer or more efficacious than monophasic OCs with the same EE content (23).

**Changes in Recommendations for Missed Pills**

The World Health Organization’s Selected Practice Recommendations for Contraceptive Use (WHOSPR) was updated in 2004 and contained revised recommendations on missed OCs. The guidelines take into consideration that when OC pills are missed, the chance of pregnancy occurring depends upon how many pills are missed, when the pills are missed, and whether the OC contains ≤30 μg of EE. The chance of pregnancy occurring is greatest when active hormonal pills are missed in a manner that extends the hormone-free OC interval (i.e., at the beginning or the end of the 21 days of active pills). Limited evidence suggests that the risk of pregnancy is greater when 20-μg EE pills are missed than when 30–35-μg EE pills are missed. The WHO guidelines are summarized in the Appendix.

**Extended OC Therapy**

Monthly withdrawal bleeding for women using hormonal contraception has been the traditional prescribing method (21 days of active pills and 7 days of placebo pills). Recently, however, this has been challenged, and the use of extended hormonal use to delay or prevent menses has been evaluated. A randomized controlled study compared a traditional 28-day cycle to an extended 49-day cycle of a 30-μg EE/300-μg norgestrel monophasic birth control regimen (24). The extended regimen resulted in fewer bleeding days and no increase in mean spotting or abnormal bleeding episodes.

There were no statistically significant differences in other reported side effects such as headaches, weight gain, cramping, or breast tenderness. Similar results have been obtained with extended use of OCs containing 20 μg of EE (25).

In 2003, the FDA approved Seasonale® (Duramed Pharmaceuticals/Barr Laboratories, Pomona, NY), a 91-day OC regimen consisting of 84 days of pills containing 30-μg EE/0.15-mg levonorgestrel and 7 hormonally inactive tablets. Seasonique™ (Duramed Pharmaceuticals/Barr Laboratories) uses the same doses of EE and levonorgestrel, but uses pills containing a 0.01 mg dose of estrogen in place of the placebo pills. It was FDA approved in 2006. A 1-year continuous extended OC regimen containing 20 μg EE/0.09 mg levonorgestrel (Lybrel®; Wyeth Pharmaceuticals) was approved by the FDA in May 2007. Lybrel consists of 1 year (365 days) of continuous active pills. The safety and side-effect profiles of Lybrel appear to be similar to those of traditional 21-day cyclic OCs. Ninety-nine percent of women resume ovulation within 3 months after discontinuing the medication.

**EMERGENCY CONTRACEPTION**

Available hormonal emergency contraceptive (EC) regimens are effective when used within 72 hours of unprotected intercourse, regardless of the stage in the menstrual cycle (26, 27). Either a combined estrogen/progestin regimen or a progestin-only treatment regimen may be used. Both regimens include two doses, the second administered 12 hours after the first. Their effectiveness appears to result primarily from an inhibition or delay of ovulation, and neither appears to interrupt or disrupt an already established pregnancy. The recommended combined estrogen/progestin treatment regimen includes 100 μg of EE and 1 mg of norgestrel or 0.5 mg of levonorgestrel. The progestin-only regimen involves a higher 0.75-mg dose of levonorgestrel.

There have been two FDA-approved and dedicated products for emergency contraception: Preven™ (four pills, each containing 50 μg of EE and 0.25 mg of levonorgestrel; two pills taken initially and two again 12 hours later; Genetics, Belle Mead, NJ) and Plan B® (two pills, each containing 0.75 mg of levonorgestrel; one pill taken initially and one 12 hours later; Duramed Pharmaceuticals/Barr Laboratories). Preven™ is no longer marketed in the United States. In August 2006, the FDA announced approval of Plan B® as an over-the-counter emergency contraceptive option for women who are 18 years of age or older. Plan B® is still a prescription-only EC for women who are less than 18 years old.

The effectiveness of the EC is determined by comparing the number of pregnancies observed after treatment to the expected number of pregnancies in the absence of treatment. In evaluating the combined EC, a meta-analysis involving more than 3000 patients observed a 74% reduction in the pregnancy rate compared with the theoretical or expected pregnancy rate (28). Less information is available regarding the success of the progestin-only regimen. The World Health Organization conducted a randomized trial in 1001 women
comparing the progestin-only regimen with the combined regimen (29). The proportion of pregnancies prevented in the progestin-only and combined regimens was 85% and 57%, respectively, with the progestin-only regimen being statistically significantly more effective (relative risk [RR] = 0.36; 95% CI, 0.18–0.70). However, it must be noted that EC is still less effective in pregnancy prevention than consistent use of other contraceptive methods. Nausea and vomiting are the predominant side effects, occurring in 42% and 16% of patients using the combined regimen, respectively (30), though these symptoms are significantly less with the progestin-only regimen (29).

Ectopic pregnancy can occur after EC, but the risk does not appear to be increased (31). There are no contraindications to EC except pregnancy, although no studies have investigated outcomes in women with contraindications to combined OC (32). The progestin-only regimen may be a better choice for women with a personal or a family history of thrombosis.

Antiprogestins have been evaluated for use as EC. Mifepristone in a single dose of 600 mg, 100 mg, 50 mg, or 10 mg is equally effective in the prevention of pregnancy and has been shown to be more effective than the combined OC regimen with fewer side effects (33–35).

**HORMONAL CONTRACEPTION AND CANCER RISK**

**Breast Cancer**

Breast cancer is very rare in young women. The cumulative risk is less than 10 per 10,000 in women of all races up to age 35 years (36). Breast cancer risk associated with OC use has been evaluated in a pooled analysis from 54 studies involving 53,297 women with breast cancer and more than 100,000 controls (37). The main finding was a small increase in the relative risk of localized breast cancer in women under age 35 associated with current OC use (RR = 1.24; 95% CI, 1.15–1.33) and also with past OC use within 1 to 4 years (RR = 1.16; 95% CI, 1.08–1.23) compared with controls. This risk declines shortly after stopping use and disappears within 10 years. By age 50, there is no difference in risk of breast cancer in ever-users of OC and controls. The study also demonstrated that breast cancers diagnosed in OC users were significantly less advanced than those in never-users (for spread of disease beyond the breast, RR = 0.88; 95% CI, 0.81–0.95). In addition, no increased risk of breast cancer was identified among women from 35 to 64 years of age who were current or former users of OCs in a large population-based, case-control study involving over 9000 women (38).

A meta-analysis (39) estimated the risk of breast cancer diagnosed before menopause in former OC users to be 1.19 (1.09–1.29) but could not take into account timing and duration of OC use. A recent analysis from the Women’s Contraceptive and Reproductive Experiences Study (40) demonstrated short-term OC use was not associated with breast cancer risk (odds ratio [OR] = 1.0; 95% CI, 0.8–1.1). Associations between OC use and breast cancer may be confounded by underlying characteristics of users or un-measured factors influencing duration of use (40). Overall, there is no evidence of any increase in lifetime risk of breast cancer among OC users.

The risk of breast cancer is increased in women whose first exposure to depot medroxyprogesterone acetate (DMPA) was within the previous 4 years and who are under age 35 years (RR = 2.19; 95% CI, 1.23–3.89) and in current users of any age who had initiated use of DMPA within the previous 5 years (RR = 2.0; 95% CI, 1.5–2.8). However, long-term, case-controlled studies do not demonstrate any increased risk of breast cancer with ever-use of DMPA or with long-term prior use (41, 42).

**Endometrial Cancer**

Oral contraceptive use is associated with a lower risk of endometrial cancer. A meta-analysis found that the incidence would be reduced by 56%, 67%, and 72% with use of combined OCs for 4, 8, and 12 years, respectively (P < .0001) (43). The lowered risk of disease persists after stopping OC use, and by 20 years it is almost 50% below that in women who have never used OCs (43).

When taken for more than 12 months, combined OCs confer equal protection against the three major histologic subtypes of endometrial cancer: adenocarcinoma, adenosquamous carcinoma, and adenocanthoma (44). Whereas earlier studies had evaluated the effect of high-dose OC preparations, a Swedish case-control study indicated that lower dose (30–35 μg) OC formulations provide comparable protection (45). Depot MPA has been shown to decrease the risk of endometrial cancer by 80%, with protective effects lasting for at least 8 years after cessation of treatment (46).

**Ovarian Cancer**

The risk of ovarian cancer declines with increasing duration of OC use. The incidence is 41%, 54%, and 61% lower with use for 4, 8, and 12 years, respectively (P < .0001) (43). The protective effects of OCs become apparent after as little as 3 to 6 months of use and continue for up to 20 years after discontinuation (47, 48). The protective effect most likely derives from the progesterin component of the combined OC (49). Risk for the four main histologic subtypes of epithelial ovarian cancer (serous, endometrioid, mucinous, and clear cell) is reduced to the same degree. The ovarian cancer risk associated with OCs containing the newer progestins, biphasic and triphasic pills, or lower dose OCs (20 μg of EE) has not yet been clearly defined but appears similar.

Oral contraceptives also may have protective benefits for women at risk for hereditary ovarian cancer (50). Continuous use for 10 years in women with a family history of ovarian cancer may reduce the risk of epithelial ovarian cancer to a level less than or equal to that observed in women with no family history of the disease (51). A case-control study involving 207 women with hereditary ovarian cancer (with BRCA1 and BRCA2 genetic mutations) and 161 of their sisters as controls.
found statistically significant protection against ovarian cancer with any past use of OCs compared with never-use (RR = 0.5; 95% CI, 0.3–0.8) (50). The greatest protection was associated with 6 or more years of use (RR = 0.3; 95% CI, 0.1–0.7).

Cervical Cancer
The use of OCs has been associated with an increased risk of cervical intraepithelial neoplasia and cervical cancer (47, 52–55). However, because the human papillomavirus (HPV) has been implicated as the main causative agent in cervical cancer (56), OC use most likely acts as cofactor in the development of this disease (55).

A recent study of pooled data from case-control studies of invasive cervical cancer (eight studies) and carcinoma in situ (two studies) evaluated the risk of cervical cancer in women who were using hormonal contraception and who tested positive for the HPV (55). Hormonal contraception for fewer than 5 years did not increase the risk of cervical cancer (OR = 0.73; 95% CI, 0.52–1.03). However, risk increased with use of hormonal contraception for 5 to 9 years (OR = 2.82; 95% CI, 1.46–5.42) and was greatest with use for 10 years or longer (OR = 4.03; 95% CI, 2.09–8.02). The proposed mechanism for this association is a hormonal effect on the cervix, a hypothesis that is supported by the increased risk of cervical cancer associated with increased parity and HPV (57) and by the correlation between higher estradiol receptor concentrations induced by OCs and the risk of low-grade cervical intraepithelial neoplasia (54).

Colorectal Cancer
There is growing epidemiologic evidence that OCs may protect women from developing colorectal cancer. In a meta-analysis, the overall estimated relative risk of colon cancer in OC users was 0.82 (95% CI, 0.74–0.92). The protection was stronger for women who had used OCs within the previous 10 years (RR = 0.46; 95% CI, 0.30–0.71) (58).

MEDICAL RISKS OF HORMONAL CONTRACEPTION

Hormonal Contraception and Bone Density
Depot medroxyprogesterone acetate use has been associated with short-term bone loss in reproductive-age women, which is attributed to the lower ovarian estrogen production resulting from suppression of gonadotropin secretion. The preponderance of evidence suggests that use of DMPA by women before they attain their peak bone mass is detrimental to bone (59–65). Cross-sectional studies have demonstrated lower bone mineral density (BMD) in the spine, hip, and distal radius of women currently using DMPA (59–62, 65). Longitudinal studies consistently demonstrate declines in hip and/or spinal BMD in women who use DMPA for 1 to 2 years compared with the BMD of nonusers over the same time period (63–65). Most of these studies involved adult users, generally older than 18 years.

Declines in BMD of 3% to 6% are seen after 24 months, correlating with the duration of treatment (66). However several studies indicate the effect is partially reversible after discontinuation of treatment and therefore may not pose any long-term risk (60, 67–69). The largest longitudinal study demonstrated that DMPA former-users and never-users had similar spine and hip BMD by 3 years after discontinuation (69). It is not yet clear if longer duration of treatment was associated with less complete recovery.

Potential adverse effects of DMPA on BMD also have been documented in adolescent women. Cross-sectional studies have suggested that the impact on BMD may be more pronounced in adolescents aged 12 to 18 years than in adults (70–73). One study demonstrated decreases in lumbar spine bone mineral of 1.5% and 3.1% in DMPA users after 1 and 2 years of use, respectively, compared with a 2.9% and 9.5% increase in controls over the same time periods (71). A reduction in spinal BMD was evident after 6 months of DMPA use and a reduction in femoral BMD after 1 year of use (71). These observations have raised concerns that DMPA use in adolescents may prevent them from achieving normal peak bone mass, although the contraceptive benefits of DMPA use in the adolescent population may outweigh any potential adverse effect on bone density (74).

In 2004, the FDA added a black box warning to Depo-Provera Contraceptive Injection and depo-subQ Provera stating that women who use DMPA “…may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of Depo-Provera Contraceptive Injection during adolescence or early adulthood, a critical period for bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture later in life. Depo-Provera Contraceptive Injection should be used as a long-term birth control method (e.g., longer than 2 years) only if other birth-control methods are inadequate” (75, 76). The physician prescribing information packet insert recommends that all patients who are using DMPA should have adequate daily intake of calcium and vitamin D and that those who need to use DMPA longer than 2 years should have their BMD evaluated. However, this recommendation is controversial. Observed short-term losses in BMD associated with DMPA are unlikely to place women at risk for osteoporosis in later years. It is not recommended to perform BMD monitoring solely in response to MPA use. Bone mineral density testing in women using DMPA should be performed only in accordance with published screening guidelines (77).

The levonorgestrel-containing contraceptive implant also has been evaluated for its effect on bone density, although data are limited. A small study in seven adolescents showed a significant increase in lumbar spine bone density over 12 months (71). Studies of forearm bone density in adults have yielded conflicting results, with both increases and decreases reported (60, 78). The levonorgestrel implant should not decrease bone density as much as DMPA because estrogen
levels are not as consistently suppressed (79), and 19-nortestosterone progestogens have a beneficial effect on bone (80).

The effect of combination OCs on bone density is not clear. Studies in postmenopausal women who have previously used OCs have revealed improved bone density that correlates with years of use (81). Reduced fracture risks that correlate with the use of high-dose formulations and use after the age of 40 also have been demonstrated in postmenopausal women (82). Short-term studies in current users of OCs containing 30 µg or 35 µg of EE have demonstrated a small gain in bone density or no significant change (60, 61, 83). One small study suggested that the gain in bone density over a 12-month period was greater with a norethindrone-containing OC compared with another containing desogestrel (61). Several recent longitudinal studies have shown detrimental effects of OCs on bone mass. In women aged 18 to 33 years, users of an OC containing 30 µg of EE and 0.15 mg of desogestrel experienced an average loss of 2.6% in lumbar spine BMD over 24 months, compared with a 2.6% increase in BMD in women who did not use hormonal contraception (63). In this same study, women using an OC containing 35 µg of EE and 1 mg norethindrone had no significant change in BMD, and users of DMPA experienced a 5.7% decrease in BMD. In a 12-month longitudinal study of adolescent girls aged 12 to 18 years using an OC containing 20 µg of EE and 0.1 mg of levonorgestrel, BMD increased less in the OC users than in adolescent girls not receiving hormonal contraception. Controls increased BMD in their femoral neck by 2.3% and in the lumbar spine by 3.8%. The OC group increased femoral neck BMD by 0.3% and lumbar spine BMD by 2.3%, and the mean percentage increase in both sites was significantly less than that seen in controls (73). In this same study, users of DMPA demonstrated reduced BMD at both sites. In the only other published study evaluating an OC containing 20 µg of EE, women aged 19 to 22 years using the OC for 5 years demonstrated no increase in lumbar spine BMD while controls demonstrated an increase of 7.8% over 5 years. This suggested that long-term treatment with OCs containing 20 µg of EE may interfere with the attainment of physiologic peak BMD (84). The majority of studies with OCs containing 30 and 35 µg of EE demonstrate either no adverse impact on BMD or a favorable effect (85–87).

The data accumulated suggest that adolescents are particularly susceptible to a negative impact of DMPA and OCs containing 20 µg of EE on bone health. Adolescents typically increase their bone mass between 2% to 10% per year, and hormonal contraception may diminish this rate of increase and contribute to a lower peak BMD in young adulthood. However, at present, it does not appear that OC use for up to 5 years is associated with any increase or decrease in fracture risk (88).

**Myocardial Infarction**

Myocardial infarction is extremely rare among reproductive-aged women. The baseline risk of myocardial infarction among healthy women rises from 0.2 per 100,000 at age 30 to 34 years to 2.0 per 100,000 at age 40 to 44 years (89). Use of low-dose OCs increases the risk of myocardial infarction by approximately two-fold among users, even after controlling for cardiovascular risk factors (including smoking, hypertension, hypercholesterolemia, diabetes, and obesity) (90). The myocardial infarction risk in OC users is increased by smoking, an effect that is more noticeable among women over age 35 years. For women under age 35 years, the incidence of myocardial infarction for smokers (3.5 per 100,000) is increased 10-fold over that for nonsmokers (0.3 per 100,000). For women aged 35 years or older, the risks of myocardial infarction are significantly higher for both smoking (40 per 100,000) and nonsmoking women (3 per 100,000) (91). Oral contraceptives should therefore be used with caution in women aged 35 years and older who smoke.

**Ischemic Stroke**

Ischemic stroke is very rare among healthy reproductive-aged women. The annual incidence rises with increasing age (6 per million at age 20 to 24 years, 10 per million at age 30 to 34 years, and 16 per million at age 40 to 44 years) (89). A summary of five epidemiologic case-control studies involving 257 exposed cases estimated that the risk of ischemic stroke was 2.2-fold higher (95% CI, 1.9–2.7) with current use of OCs containing <50 µg of EE compared with nonusers. The risk is not related to the progestin component of OCs (92). Similar increased risk has been noted in other studies (93, 94). In contrast, a smaller pooled analysis of two U.S. case-controlled studies did not show an increased risk of ischemic stroke in current users of low-dose OCs compared with nonusers except in the subgroup of women who experience migraine headaches (95).

Although the risk of stroke associated with migraine without an aura is not consistently demonstrated, many studies have demonstrated an increased risk of stroke in women who have a migraine with aura (95–98). An aura is a reversible visual symptom that precedes a migraine headache, including flickering zigzag lines and scintillating scotomata. The occurrence of only blurred vision is not considered an aura. Some studies suggest that the risk of ischemic stroke associated with OCs is not significantly different in women with simple migraine (no aura) compared with those with classic migraine (with aura) (93, 94, 99). The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Use demonstrated that type of migraine did not affect the risk of stroke in migraineurs who used OCs (93). Other evidence suggests that OC use combined with history of migraine headache confers a two-fold to four-fold greater risk of stroke than does history of migraine and nonuse of OCs (100). Oral contraceptives should not be used in patients with visual aura or focal neurologic deficits associated with migraine headache (i.e., weakness, speech deficits). Similarly, OCs should not be used in women who have migraine without aura if they smoke or are aged 35 or older because smoking significantly increases the risk of stroke (93).
**Hemorrhagic Stroke**

The incidence of hemorrhagic stroke among healthy women is low but increases with age from 32 to 46 per 100,000 woman-years for ages 20 to 24 years, 30 to 34 years, and 40 to 44 years, respectively (89). Oral contraceptive use is associated with a three-fold higher risk of hemorrhagic stroke compared with nonusers (RR = 1.0; 95% CI, 0.7–1.5). However, studies have suggested that the risk of hemorrhagic stroke is far less than that associated with OC formulations containing progesterins (desogestrel and gestodene compared with levonorgestrel) (102).

The FDA has suggested no change in prescribing (66). Oral contraceptives containing the progestin norgestimate are associated with risks of nonfatal VTE that are similar to OCs containing levonorgestrel and below that of OCs containing desogestrel. The incidence rates of nonfatal VTE per 100,000 woman-years for women using formulations containing desogestrel or gestodene (103). The risk remained significantly elevated for short-term and long-term users and for users of differing ages, but is far less than that associated with pregnancy. Although the risk of VTE is statistically significant, it is still a rare event and would translate to one to two cases per 10,000 women-years of use (104).

The risk of VTE associated with prothrombotic conditions is further increased with OC use. The most common of these is the factor V Leiden mutation, which results in resistance to activated protein C. The risk of VTE in women who are heterozygous for the mutation is seven-fold higher than in non-carriers. In women who are homozygous for the mutation and use OCs, the risk was 35-fold higher (95% CI, 7.8–154) in one report (106) but only 10-fold higher in another (107). The prevalence of the factor V Leiden mutation is 5% in Caucasians but extremely low in Asian and African populations (108). A genetic defect in prothrombin also is associated with increased risk of VTE, and increases the risk of VTE in users of OCs (109). Other known factors involved in the development of VTE include protein C, protein S, and antithrombin III deficiencies (106). The presence of more than one of these mutations increases the risk of VTE significantly. Oral contraceptives should not be used by women who carry these mutations. At this time, screening for the factor V Leiden mutation before initiating OC use is recommended only for women who have a personal or family history of thrombosis (106). Even with the increased risk conferred by factor V Leiden and other genetic mutations, the majority of carriers who use OCs will never develop a clinical VTE.

**Venous Thromboembolism**

The incidence of VTE among healthy women is low but increases with age from 32 to 46 cases per million per year for ages 20 to 24 years, 30 to 34 years, and 40 to 44 years, respectively (89). Oral contraceptive use is associated with a three-fold higher risk of VTE (89). The risk appears to be proportional to the estrogen dose (101). However, studies also have suggested that the risk of VTE is less than two-fold higher than that associated with OC formulations containing the newer progestins (desogestrel and gestodene compared with levonorgestrel) (102).

A meta-analysis including three cohort and nine case-control studies of VTE risk associated with newer progestins yielded an overall adjusted odds ratio for VTE of 1.7 (95% CI, 1.4–2.0) with an absolute excess risk of 1.5 events per 10,000 woman-years (106). The presence of more than one of these mutations increases the risk of VTE significantly. Oral contraceptives should not be used by women who carry these mutations. At this time, screening for the factor V Leiden mutation before initiating OC use is recommended only for women who have a personal or family history of thrombosis (106). Even with the increased risk conferred by factor V Leiden and other genetic mutations, the majority of carriers who use OCs will never develop a clinical VTE.

**SUMMARY AND CONCLUSIONS**

- Hormonal contraception is a safe and effective form of reversible contraception.
- New transdermal, injectable, vaginal, and implantable delivery methods appear to have safety and efficacy comparable to that of OCs.
- Modifications of OCs, including extended use of active pills, progressively lower doses of estrogens, and the development of newer progestins, have maintained contraceptive efficacy while potentially reducing the incidence of side effects.
- Emergency contraception using either combined estrogen/progestin or progestin-only regimens is effective in reducing the risk of pregnancy from unprotected intercourse. The progestin-only regimen may be more effective and have fewer side effects.
- Use of depot medroxyprogesterone acetate and OCs containing 20 μg of ethinyl estradiol are associated with a small reduction in bone mineral density.
- Past and current use of OCs decreases the incidence of endometrial and ovarian cancers.
- Longer durations of OC use have the potential to increase the risk of cervical cancer. Oral contraceptives may act as a cofactor for HPV in the development of cervical cancer.
- Past or present OC use is not associated with any increase in lifetime risk of breast cancer. Among women younger than 35 years, a small reversible increased risk of breast cancer is seen after 4 years of use. No increased risk has been observed in women 35 to 64 years of age.
- The risk of stroke and myocardial infarction in reproductive-aged women is low but is increased in OC users over age 35 who smoke.
- The risk of VTE is increased in OC users and higher in carriers of mutations resulting in prothrombotic conditions. At this time, screening for inherited thrombophilias before treatment with OCs is recommended only for women having a personal or a significant family history of thrombosis.

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REFERENCES


96. S112
Summary of the World Health Organization's practice guideline for contraceptive use regarding missed oral contraceptive pills.

### For women taking 30–35 μg ethinyl estradiol pills
A woman who has missed 1 or 2 active (hormonal) pills or starts a pack 1 or 2 days late should:
- Take an active (hormonal) pill as soon as possible* and then continue taking pills daily, 1 each day.
- No additional contraceptive protection is recommended.

A woman who has missed 3 or more active (hormonal) pills or starts a pack 3 or more days late should:
- Take an active (hormonal) pill as soon as possible* and then continue taking pills daily, 1 each day.
- Use condoms or abstain from sex until she has taken active (hormonal) pills for 7 days in a row.
- If the missed pills occur in the third week, finish the active (hormonal) pills in the current pack and start a new pack the next day. She should not take the 7 inactive pills.
- If the missed pills occur in the first week and unprotected sex has occurred, consider the use of emergency contraception.

### For women taking ≤ 20 μg ethinyl estradiol pills
A woman who has missed 1 active (hormonal) pill or starts a pack 1 day late should:
- Take an active (hormonal) pill as soon as possible* and then continue taking pills daily, 1 each day.
- No additional contraceptive protection is recommended.

A woman who has missed 2 or more active (hormonal) pills or starts a pack 2 or more days late, should take an active (hormonal) pill as soon as possible* and then continue taking pills daily, 1 each day.
- Use condoms or abstain from sex until she has taken active (hormonal) pills for 7 days in a row.
- If the missed pills occur in the third week, finish the active (hormonal) pills in current pack and start a new pack the next day. Should not take the 7 inactive pills.
- If the missed pills occur in the first week and unprotected sex has occurred, consider the use of emergency contraception.

### For women taking either 30–35 μg or ≤ 20 μg ethinyl estradiol pills
A woman who has missed any inactive (nonhormonal) pills should:
- Discard the missed inactive (nonhormonal) pill(s) and then continue taking pills daily, 1 each day.


* A woman should take 2 pills on the same day (one as soon as she remembers and the other at the regular time) or can take both pills at the same time. She should then continue taking the rest of the pills daily. A woman may either discard any additional pills to stay on schedule, or can continue to take 1 pill daily until all active (hormonal) pills are gone.