Update on contraception: Benefits and risks of the new formulations

ABSTRACT

Several new contraceptives have become available to women in recent years. These new agents include ultra-low-dose oral contraceptives as well as injectable, vaginal, and patch formulations. We review these, with emphasis on the Yasmin pill (which contains a new progestin), the Lunelle once-a-month injection, the Ortho Evra patch, the NuvaRing vaginal ring, the Mirena intrauterine device, and emergency contraceptive kits. Patient education regarding these options is essential for patient compliance and satisfaction.

KEY POINTS

Contraception is used both for protection against unwanted pregnancy and for a variety of noncontraceptive health benefits, including improvements in dysmenorrhea, anemia, acne, and others.

Various drugs, including some antibiotics, anticonvulsants, anti-HIV protease inhibitors, and herbal products, can affect the metabolism of oral contraceptives.

Blood pressure should be closely monitored for several months after a woman starts taking oral contraceptives, and followed yearly thereafter.

If an Ortho Evra contraceptive patch becomes partially or completely detached, the patient should replace it immediately, but if it has been off for more than 1 day she may not be protected against pregnancy.

OVERVIEW OF ORAL CONTRACEPTIVES

Oral contraceptives have been used for more than 40 years in the United States and are the second most popular contraceptive choice for women (after sterilization).2 About 35 million women in the United States use some form of contraception, and 95% of all sexually active women have used it at some point.3,4 Contraception is used both for protection against unwanted pregnancy and, in the case of oral contraceptives, for

This paper discusses therapies that are experimental or that are not approved by the US Food and Drug Administration for the use under discussion.
Most oral agents contain both estrogen and progestin, which suppress gonadotropins, inhibit ovulation, and alter cervical mucus to make sperm entry difficult.

In theory, the failure rate is 0.1%, but the true failure rate is 3% due to incorrect use.

**Estrogen dosing: Low or ultra low**

The two estrogen compounds available in the United States are ethinyl estradiol and mestranol. Ethinyl estradiol is the most commonly used; mestranol is a prodrug that is converted to ethinyl estradiol by the liver. Products containing mestranol do not contain less than 50 μg because lower doses are less effective.

Although early oral contraceptives containing ethinyl estradiol had up to 100 μg, current pills contain an average of 30 to 35 μg. Pills containing less than 50 μg of ethinyl estradiol are called “low-dose.”

New “ultra-low-dose” pills contain ethinyl estradiol 20 to 25 μg (Table 1, Table 2). They are used mainly during the menopausal transition to control symptoms and for contraception, but they also can be used in patients who have adverse effects with higher doses.

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**TABLE 1**

**Monophasic oral contraceptives**

<table>
<thead>
<tr>
<th>PRODUCTS</th>
<th>ESTROGEN</th>
<th>PROGESTIN</th>
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</thead>
<tbody>
<tr>
<td>Necon 1/50, Nelova 1/50 M, Norinyl 1+50, Ortho-Novum 1/50</td>
<td>Mestranol 50 μg</td>
<td>Norethindrone 1.0 mg</td>
</tr>
<tr>
<td>Demulen 1/50, Zovia 1/50</td>
<td>Ethinyl estradiol 50 μg</td>
<td>Ethynodiol diacetate 1.0 mg</td>
</tr>
<tr>
<td>Ovral, Ogestrel</td>
<td>Ethinyl estradiol 50 μg</td>
<td>Norgestrel 0.5 mg</td>
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<tr>
<td>Ovcon-50</td>
<td>Ethinyl estradiol 50 μg</td>
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**LOW-DOSE**

<table>
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<tr>
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<tr>
<td>Demulen 1/35, Zovia 1/35</td>
<td>Ethinyl estradiol 35 μg</td>
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<td>Brevicon, Modicon, Necon 0.5/35, Nelova 0.5/35, Nortrel 0.5/35</td>
<td>Ethinyl estradiol 35 μg</td>
<td>Norethindrone 0.5 mg</td>
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<table>
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<tr>
<th>PRODUCTS</th>
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<tr>
<td>Ovcon-35</td>
<td>Ethinyl estradiol 35 μg</td>
<td>Norethindrone 0.4 mg</td>
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<td>Ortho-Cyclen</td>
<td>Ethinyl estradiol 35 μg</td>
<td>Norgestimate 0.25 mg</td>
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<td>Apri, Desogen, Ortho-Cept</td>
<td>Ethinyl estradiol 30 μg</td>
<td>Desogestrel 0.15 mg</td>
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<td>Yasmin</td>
<td>Ethinyl estradiol 30 μg</td>
<td>Drospirenone 3.0 mg</td>
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<tr>
<td>Levlen, Levora, Nordette</td>
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<td>Levonoregestrel 0.15 mg</td>
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<td>Loestrin 1.5/30</td>
<td>Ethinyl estradiol 30 μg</td>
<td>Norethindrone acetate 1.5 mg</td>
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<tr>
<td>Lo/Ovral, Low-Ogesteral</td>
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**ULTRA-LOW-DOSE**

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<td>Alesse, Aviane, Levlite</td>
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<td>Levonorgestre 0.1 mg</td>
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<td>Loestrin 21 1/20</td>
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**PROGESTIN-ONLY**

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<tr>
<td>Ovette</td>
<td>—</td>
<td>Norgestrel 0.075 mg</td>
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<tr>
<td>Ortho Micronor, Nor-Q.D.</td>
<td>—</td>
<td>Norethindrone 0.35 mg</td>
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The new progestins

In the 1940s, chemists made structural changes to testosterone that altered its activity from an androgen to a progestin. Testosterone-derived progestins bind to the androgen receptor and have varying degrees of androgenic activity.

Adverse metabolic effects of highly androgenic progestins (eg, levonorgestrel) include reductions in serum high-density lipoprotein (HDL), increased low-density lipoprotein (LDL), and glucose intolerance. More-selective, third-generation progestins were developed with structural modifications to lower their androgen activity; examples are norgestimate and desogestrel.

The efficacy of oral contraceptives that contain the new progestins is similar to that of the older formulations. Compared with levonorgestrel-containing pills, which are the most androgenic of the second-generation oral contraceptives, the third-generation pills have less of an effect on carbohydrate and lipid metabolism and are more effective in reducing acne and hirsutism in hyperandrogenic women (TABLE 3).

Unfortunately, data are limited comparing the third-generation progestins with second-generation progestins such as norethindrone and ethynodiol diacetate (which are less androgenic than levonorgestrel). Furthermore, controversy has arisen because of reports of...
increased risk of deep venous thrombosis with third-generation pills compared with second-generation pills.6

Given this debate, our approach is to prescribe pills containing norethindrone, a less androgenic second-generation progestin, when starting a patient on an oral contraceptive for the first time. However, women doing well on a third-generation progestin do not need to change preparations.

Monophasic or multiphasic?
To further lower the total steroid dose, in the late 1970s pharmaceutical companies introduced multiphasic preparations—pill packs that vary the dose at different times in the menstrual cycle (TABLE 2). Trials have not consistently shown significant differences between monophasic, biphasic, and triphasic oral contraceptives regarding bleeding pattern, symptoms, or efficacy, however.7

Because most clinical experience and available studies are with the monophasic formulations, these are often preferred. However, as for patient satisfaction, our clinical observation is that the choice of progestin is probably more important than whether the regimen is monophasic or multiphasic.

Progestin-only contraceptives
Progestin-only oral contraceptives, otherwise known as “mini-pills,” are available for women who cannot tolerate estrogen (eg, due to a history of heart disease or thromboembolism). These pills, however, are associated with more breakthrough bleeding and lower contraceptive efficacy than combination pills, and they are used mainly in lactating women. In fact, a backup contraceptive method must be used for 2 days if a woman is more than 3 hours late taking a dose. A backup method also is recommended each month at midcycle to improve efficacy.

In addition, progestin-only contraceptives, such as injectable medroxyprogesterone acetate (Depo-Provera), have recently been linked to reversible decreases in bone density.8,9 The potential role of these agents in osteoporosis risk is still being defined. For this reason, women taking progestin-only agents should be sure to take in at least 1,200 mg of calcium daily.

Drug interactions
Various drugs can influence the metabolism of oral contraceptives. Unintended pregnancy or breakthrough bleeding can result when oral contraceptives are taken with:

- Antimicrobials (eg, penicillins, tetracyclines, griseofulvin, rifampin)
- Anticonvulsants (eg, phenytoin, carbamazepine, felbamate, topiramate)
- Anti-HIV protease inhibitors
- Herbal products. For example, in women taking oral contraceptives and St. John’s wort (Hypericum perforatum), bleeding irregularities may occur 1 week after starting St. John’s wort, with regular cycles returning when the herb is stopped.10

The incidence of accidental pregnancy in women taking these medications with oral contraceptives is unknown, but women using the lowest-dose preparations may be at highest risk. This is an important consideration, given the large number of ultra-low-dose regimens on the market (TABLE 1).11

Safety of oral contraceptives
The safety profile of oral contraceptives has been demonstrated in millions of women, and taking them is considered safer than pregnan-
A recent study found similar mortality rates in 23,000 users and nonusers of oral contraceptives.

**Noncontraceptive benefits of oral contraceptives**

Most women are unaware of the many noncontraceptive benefits of oral contraceptives, which include improvements in or decreased risk of:

- Dysmenorrhea
- Anemia
- Acne
- Hirsutism
- Ectopic pregnancy
- Benign breast disease
- Endometrial cancer
- Ovarian cysts
- Ovarian cancer (newly recognized: a 50% decrease in ovarian cancer risk, including cases associated with mutations in the BRCA genes)
- Colorectal cancer (an 18% to 40% reduction)
- Pelvic inflammatory disease (a 10% to 70% lower incidence)
- Osteopenia, osteoporosis. Because oral contraceptives provide a consistent dose of estrogen, they may increase bone mineral density by promoting higher peak bone mass. This benefit has been reported with ultra-low-dose formulations, and the positive effect increases with higher doses and longer use. A 25% reduction in hip fractures has been demonstrated.
- Dyslipidemia. Oral contraceptives that contain third-generation progestins improve serum lipoprotein profiles by increasing HDL and decreasing LDL, although the clinical significance of these changes is not clear.

**Risks of oral contraceptive use**

The benefits of oral contraceptives must be weighed against the potential risks.

**Coronary artery disease.** Low-dose oral contraceptives were developed in response to increased cardiovascular events associated with higher-dose oral contraceptives. Studies of oral contraceptives with less than 50 μg estrogen have found no increased risk of myocardial infarction (MI) among healthy, nonsmoking women.

In women over age 35, smoking 15 or more cigarettes per day increases the risk of MI. Studies have not defined how other cardiovascular risk factors affect the incidence of MI in oral contraceptive users. Concomitant hypertension, dyslipidemia, diabetes, or obesity may further increase the risk.

**Venous thromboembolism.** Studies consistently show that the risk of venous thromboembolism (VTE) is two to six times higher in oral contraceptive users than in nonusers. However, the incidence of VTE in otherwise healthy women is low, at about 1 or 2 persons in 1,000 to 10,000, depending on age. The primary factor contributing to VTE is estrogen; however, there are conflicting reports about the potentially additive risk with the third-generation progestins.

Risk factors for VTE include increasing age, obesity, family history of VTE, surgery, and the factor V Leiden mutation. Patients with this mutation have six to seven times the risk of VTE, which increases up to 35 times with oral contraceptive use. Women with a documented history of VTE that is unexplained or associated with pregnancy should avoid oral contraceptives.

**Hypertension.** Many women have an increase in blood pressure with oral contraceptive use, although readings usually remain within the normal range. The risks of pregnancy in women with hypertension should be weighed against the risks of oral contraceptive use.

Low-dose oral contraceptives are not contraindicated in otherwise healthy women with well-controlled hypertension, but women over age 35 who have hypertension and who smoke or have end-organ vascular disease should not use oral contraceptives.

Blood pressure should be closely monitored for several months after starting oral contraceptives and followed yearly thereafter.

**Stroke.** Studies evaluating oral contraceptives and stroke are difficult to interpret. Most studies were small, did not differentiate between hemorrhagic and thromboembolic stroke, and did not control for major risk factors. Most evidence suggests that there is no increased risk in oral contraceptive users, except in those who smoke.

The risk of stroke from use of these agents...
in migraine patients also is controversial. Studies of older, high-dose oral contraceptives showed an increased risk of stroke, whereas studies of low-dose formulations have not.29

**Breast cancer.** Evidence of a possible link between breast cancer and hormone exposure has been inconsistent.

A meta-analysis30 of 54 studies that included a total of 53,000 women with breast cancer and 100,000 controls found that the relative risk of breast cancer in current users of oral contraceptives was 1.24. After the oral contraceptive was stopped, this risk decreased and was absent after 10 years. Breast cancers that were diagnosed while the patient was taking an oral contraceptive tended to be less advanced.

On the other hand, a recent case-control study31 found that, in women aged 35 to 64 years, current or former oral contraceptive use was not associated with a significantly increased risk of breast cancer.

In women with a family history of breast cancer in a first-degree relative, high-dose formulations (used before 1975) may further increase this risk, although the newer low-dose formulations have not been shown to carry this increased risk.32

In patients with a BRCA1 or BRCA2 mutation, the potential increased risk of breast cancer needs to be weighed against the decreased risk of ovarian cancer. These patients should consider discussing the safety of oral contraceptives with a consultant, such as a geneticist or a specialist in women’s health or breast health.

**Cervical cancer.** For every 100,000 women who use oral contraceptives for longer than 8 years, 30 to 125 additional cases of cervical cancer may occur. However, oral contraceptive users may have more unprotected sexual encounters and an increased exposure to the human papillomavirus, a known risk factor for cervical cancer.

The slightly increased risk of cervical cancer needs to be weighed against the roughly 50% reduction in the risks of ovarian and endometrial cancers. One model estimated that for every 100,000 women, 44 fewer reproductive cancers would occur in users than in nonusers.33

### NEW CONTRACEPTIVE OPTIONS

#### The Yasmin pill: Ethinyl estradiol plus a spironolactone analogue

Yasmin is a low-dose, monophasic oral contraceptive containing ethinyl estradiol and drospirenone, a progestin analogue of spironolactone.34 Drospirenone is the only progestin with both antimineralocorticoid and antiandrogenic properties that is approved by the US Food and Drug Administration (FDA).

**Effectiveness.** Yasmin is 99% effective, which is similar to other oral contraceptives.35

**Advantages.** Due to its antiandrogenic diuretic properties, Yasmin has the added benefit of improving acne, seborrhea, and hirsutism as well as providing good weight stability—or even slight weight loss—from decreased water retention.

An 8-month study36 compared weight gain in 80 women taking either Yasmin or ethinyl estradiol and levonorgestrel (0.15 mg). Women taking Yasmin lost an average of 1.8 lb (0.8 kg), while women taking ethinyl estradiol and levonorgestrel gained an average of 1.5 lb (0.7 kg).

Yasmin may benefit women with premenstrual symptoms such as bloating.37,38

**Practical considerations.** The 3 mg of drospirenone in each pill is equivalent to 25 mg of spironolactone, a potassium-sparing diuretic. Therefore, the serum potassium level should be checked during the first month of therapy.

Yasmin should be used with caution in women taking medications that can lead to hyperkalemia, such as other potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, aldosterone antagonists, and nonsteroidal anti-inflammatory drugs. It is contraindicated in women with renal, hepatic, or adrenal insufficiency.

#### Ortho Evra: ‘The patch’

In 2001, the FDA approved the first transdermal contraceptive patch, Ortho Evra (20 μg ethinyl estradiol and 150 μg norelgestromin per 24 hours).39 Norelgestromin is a metabolite of norgestimate, the progestin in the third-generation pills Ortho-Cyclen and Ortho Tri-Cyclen.

**Effectiveness and advantages.** Three
clinical trials have been conducted worldwide involving 4,578 women, 3,319 of whom used Ortho Evra. Compared with daily oral contraceptives, the patch offered similar safety, contraceptive efficacy, and menstrual cycle control and had the added benefit of improved compliance. It is hoped that improved compliance will lead to decreased failure rates.

Practical considerations. In clinical trials, most unintended pregnancies were in women weighing more than 198 lb (90 kg), suggesting that Ortho Evra may be less effective in women heavier than this weight. Therefore, Ortho Evra should be used with caution in these women.

The most common adverse effects in clinical trials were, in decreasing order, breast tenderness, headache, skin irritation, and nausea. It is unknown if the risk of VTE with Ortho Evra is different than with oral contraceptives.

The patient should start Ortho Evra on the first day of her menstrual period (or first day of withdrawal bleeding in oral contraceptive users). A new patch is applied weekly, on the same day each week, for 3 weeks. Week 4 is patch-free, and withdrawal bleeding is expected during this time. As with the oral contraceptives, there should not be more than a 7-day hormone-free interval between dosing cycles.

The patch should be applied to clean, dry skin on the buttocks, upper outer arm, lower abdomen, or upper torso (excluding breasts). Ortho Evra should not be placed on skin that is red or irritated or where it will be rubbed by tight clothing. Oils, creams, or cosmetics should not be applied near the patch. The patient should be encouraged to participate in her usual physical activities (eg, sauna, whirlpool, swimming).

If the patch comes off. Of more than 70,000 Ortho Evra patches worn, 4.7% were replaced because they either fell off (1.8%) or were partly detached (2.9%).

If the patch is detached, a new one should be applied immediately. Supplemental adhesives or wraps should not be used.

If a patch is partially or completely detached for less than 1 day, the patient should replace it with a new patch immediately. No back-up contraception is needed.

If a patch is detached for more than 1 day or if the woman is unsure how long it has been detached, she may not be protected from pregnancy. She should stop the current contraceptive cycle and start a new cycle immediately by applying a new patch.

Packages of single replacement patches are available. Used patches still contain active hormones, so they should be folded in half before they are discarded.

Lunelle: The ‘once-a-month shot’
Lunelle, the first monthly, injectable combination hormone, contains estradiol cypionate and medroxyprogesterone acetate. The other injectable birth control method, Depo-Provera, contains medroxyprogesterone acetate only and is given intramuscularly every 3 months.

Effectiveness. The efficacy rates of Depo-Provera and Lunelle are comparable. Lunelle is effective for contraception during the first cycle of use.

Unexpected pregnancies occurring in women receiving Lunelle are uncommon and so far have not shown congenital malformations.

Compared with Ortho-Novum 7/7/7, Lunelle had similar efficacy, although women using Lunelle were more likely to experience irregular bleeding at the end of the first year. Weight gain was the most common adverse effect that led to discontinuation of Lunelle (5.7% compared with 0.9% in the Ortho-Novum 7/7/7 group). Women gained an average of 4 lb during the first year and an additional 2 lb during the second year. Other side effects are similar to those of oral contraceptives, including irregular menstrual cycles, nausea, bloating, and breast tenderness.

Advantages. This agent is a good option for women in whom there are concerns about compliance.

Practical considerations. The first injection should be given within the first 5 days of menses, and subsequent injections are given within 28 to 30 days of the previous injection. If more than 33 days have passed since the last injection, pregnancy must be ruled out before another injection is given. Patients switching to Lunelle from oral contraceptives should get their first injection within 7 days of their last active pill.
Lunelle is comparable in cost to other oral contraceptives, but patients must go to a nurse or pharmacist every month to get the injection, which may add to the cost. Due to concerns about subpotency, pre-filled syringes of Lunelle were recalled in October 2002. Lunelle packaged in standard vials was not affected by this recall and is still available.

**NuvaRing: A once-a-month vaginal ring**

NuvaRing is a contraceptive vaginal ring that releases 120 µg of etonogestrel and 15 µg of ethinyl estradiol daily. It is colorless and odorless and measures 2 inches in diameter, with a cross-sectional diameter of 4 mm.

The ring is easy for patients to insert and is left in place for 3 weeks. Withdrawal bleeding occurs during the fourth, ring-free week.

**Efficacy.** NuvaRing is comparable to oral contraceptives in efficacy.

**Advantages.** NuvaRing is an excellent choice for most women, although it is not recommended if a cystocele, rectocele, or uterine prolapse is present. One of its main advantages is convenience.

A recent study of 247 women compared cycle control and tolerability of NuvaRing vs a standard combined oral contraceptive containing ethinyl estradiol 30 µg and levonorgestrel 150 µg. Both groups experienced withdrawal bleeding; however, the incidence of irregular bleeding in the NuvaRing group was significantly less than in the oral contraceptive group. In addition, NuvaRing users had a higher incidence of normal intended bleeding patterns compared with the oral contraceptive group. The tolerability of both contraceptives was good, although the NuvaRing users had a higher incidence of vaginal discomfort and vaginitis.

**Practical considerations.** If the ring is out of the vagina for more than 3 hours during the first 3 weeks of the cycle, effective contraception cannot be guaranteed. The ring should be rinsed with warm water and reinserted within 3 hours to maintain efficacy.

If a woman forgets to remove the ring after 3 weeks, it will continue to inhibit ovulation for up to 5 weeks.

**Mirena: The progestin IUD**

Mirena, an intrauterine device (IUD), has been used since the early 1980s in other countries for contraceptive and noncontraceptive purposes. It recently was approved for contraceptive use in the United States.

Mirena is a levonorgestrel-releasing system that is effective for up to 5 years. It acts locally on the endometrium with progestogenic effects and may also thicken cervical mucus and inhibit sperm capacitation and survival.

**Effectiveness.** Mirena is 99% effective. A study in 1,169 women found that pregnancy rates over 1 year and 5 years were less than 1%. Of the unwanted pregnancies, half were ectopic. This translates into an annual incidence of one ectopic pregnancy per 1,000 users, which is not significantly different than the rate of ectopic pregnancies in sexually active women not using any contraception.

**Advantages.** Mirena’s delivery of progesterone to the endometrium results in less bleeding than with copper IUDs. Some women, however, may have irregular bleeding during the first 3 to 6 months. After that, bleeding usually declines, and 20% of women have amenorrhea by the end of the first year.

The decreased bleeding profile and 5-year efficacy of Mirena make it an attractive option, especially for women with menorrhagia or those who desire long-term contraception.

**EMERGENCY CONTRACEPTION**

Postcoital (emergency) contraception is defined as the prevention of pregnancy within 72 hours of unprotected intercourse or failure of a contraceptive method (eg, a broken condom).

Even though emergency contraception is known to be effective and has a low potential for adverse effects, many patients are not prescribed it because their physicians either do not know about it or are not comfortable with its use. Until recently, the most commonly prescribed regimens included:

- Ethinyl estradiol 2.5 mg twice a day for 5 days
- Ethinyl estradiol 100 µg and levonorgestrel
0.5 mg, repeated in 12 hours
• Levonorgestrel 0.75 mg, repeated in 12 hours

Recently, the FDA approved two emergency contraceptive kits. The Preven kit contains a pregnancy test to exclude pregnancy before taking the pills, which each contain ethinyl estradiol 50 µg and levonorgestrel 0.25 mg. The patient takes two pills and another two in 12 hours.

The Plan B kit is similar, but contains progestin only, thus causing less nausea and vomiting than regimens that also contain estrogen.46 One tablet of Plan B should be followed by a second dose within 12 hours.

These regimens have similar efficacy, reducing the number of pregnancies by 89%; however, if Plan B is taken in the first 24 hours, it can prevent 95% of expected pregnancies.

The most significant side effect of these regimens is nausea; therefore, an antiemetic can be prescribed concomitantly.

Mifepristone (Mifeprex; RU-486) in a single 600-mg dose, has higher efficacy than the previously mentioned regimens, as well as a lower incidence of adverse effects.47 However, it is not FDA-approved for emergency contraceptive use in the United States.

A copper IUD also can be used as emergency contraception if placed within 120 hours of unprotected intercourse, although this is not commonly done in the clinical setting.

# REFERENCES

4. Forrest JD. Has she or has she not? US women’s experience with contraception. Fam Plann Perspect 1987; 19:133.

# ESSURE: AN EXPERIMENTAL DEVICE FOR SURGERY-FREE STERILIZATION

Currently, the only option for women who want permanent birth control is tubal ligation, a surgical procedure that requires anesthesia and several days of recovery.

The Essure device is a mesh embedded in coils that causes scar tissue and stricture of the fallopian tubes. It is inserted through a hysteroscope and requires no incision and minimal anesthesia. This device is awaiting FDA approval and may be available this year. Long-term data are unavailable.

# THE WOMAN SHOULD CHOOSE THE RIGHT OPTION FOR HER LIFESTYLE

Many effective contraceptive methods offer both contraceptive and noncontraceptive benefits. Low-dose oral contraceptives are safe, effective, and popular. Injectable, implantable, and transdermal formulations are available for women who have difficulties with compliance. Progestin-only contraceptive options are alternatives, especially for women who cannot take or tolerate estrogens.

The best contraceptive choice for each woman is the method that she feels the most comfortable with and that suits her lifestyle. Women should be educated about the various forms of contraception and encouraged to choose one that best meets their needs and desires. This, in turn, will improve patient satisfaction and compliance.


