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# Review of newer contraceptive agents

## ABSTRACT

Advances in contraceptive technology have made birth control more effective, convenient, and safe. We review the newer products and some under development, including the latest oral contraceptives, injectable progesterone, subdermal progestin implants, progesterone-releasing IUDs, emergency contraception, and male contraception.

## KEY POINTS

Newer oral contraceptives contain much lower doses of estradiol than older preparations and use newer progestins with less androgenic activity. They therefore cause fewer side effects.

Depomedroxyprogesterone acetate injections every 3 months are a good contraceptive option for women in whom compliance may be low.

Progestin implants have a failure rate of 0.8 per 100 woman-years for the first 5 years of use, increasing to 2 per 100 woman-years by the 6th year. The implants should be removed after 5 years.

Progesterone-releasing IUDs reduce the cramping and increased menstrual bleeding that often occur with nonmedicated IUDs.

**T**WO THIRDS of reproductive-age women use some form of contraception, yet 55% of the 6.3 million pregnancies each year in the United States are unplanned, and half of these result in abortion.

Physicians should discuss contraception with all sexually active patients of childbearing age. Safe and effective contraceptive agents are available, but need to be adequately provided to at-risk populations.

In this review we focus on the latest improvements in oral contraceptives, long-acting contraceptives such as injectable suspensions and subdermal implants, and medicated intrauterine devices (IUDs). Advances in emergency postcoital contraception are also reviewed.

## ORAL CONTRACEPTIVES

Oral contraceptives, the most popular method of reversible contraception in the United States,<sup>1</sup> are highly effective, with a failure rate of 0.3 pregnancies per 100 woman-years of typical use, or 0.1 per 100 woman-years of ideal use.

### Mechanism of action

Used singly in high doses, both estrogens and progestins can hinder ovulation but may cause side effects such as breakthrough bleeding, endometrial hyperplasia, acne, and weight gain. Used in combination, they act synergistically and suppress ovulation at much lower doses, with fewer side effects.

These hormones work in several ways. Ethinyl estradiol diminishes follicle-stimulating hormone (FSH) secretion, leading to impaired follicular maturation and insufficient estrogen production via the ovaries. Progestins primarily inhibit luteinizing hormone (LH) secretion and thus ovulation. In addition, progestins thicken the cervical mucus (mak-



ing it impermeable to sperm) and also cause endometrial atrophy, thereby making implantation improbable.

### Improvements in newer preparations

Several refinements have made oral contraceptives much safer and better tolerated than when they were introduced in 1960, while maintaining their high rate of effectiveness:

**Lower estrogen doses.** Early oral contraceptives contained up to 150 µg of the estrogen ethinyl estradiol; newer preparations contain only 20 to 50 µg. The side effects of estrogen increase with the dose and are less common with the lower-dose preparations. On the other hand, breakthrough bleeding is seen more often with the low-dose preparations but may also be due to missing pills or endometritis.

**Improved progestins.** Progestins are synthetic derivatives of testosterone, manipulated to be highly progestogenic and less androgenic. The progestins used in oral contraceptives have evolved through three generations (TABLE 1) and now have very little androgenic activity.

**Phasic preparations.** Whereas older oral contraceptives contain the same amount of estrogen and progestin in each tablet and are taken for 21 consecutive days in a 28-day cycle, some newer ones are phasic—ie, they vary the dose of progestin to achieve fewer metabolic side effects. Pills that vary the estrogen dose (Estrostep 21) are also available—in theory, these reduce the occurrence of breakthrough bleeding. A new formulation (Mircette) containing 10 µg of ethinyl estradiol during days 22 through 26 of the 28-day pack is now available and should reduce breakthrough ovulation as well as breakthrough bleeding.

### Estrogen-related side effects

Although estrogens can cause nausea, breast tenderness, headache, decreased libido, depression, and cyclic weight gain, their most serious potential side effect is venous thromboembolism. Use of current oral contraceptives is not considered a risk factor for cardiovascular disease or breast cancer.<sup>2</sup>

**Venous thromboembolism.** Estrogen alters the synthesis of coagulation factors and

**TABLE 1**

## Progestins used in oral contraceptives

### First generation (no longer in use)

Ethisterone

### Second generation

Ethinodiol

Levonorgestrel

Norethindrone

Norethindrone acetate

Norgestrel

### Third generation (since 1992)

Desogestrel

Gestodene (not available in the United States)

Norgestimate

fibrinolytic enzymes, making thrombosis more likely. The higher the dose, the greater the risk.<sup>3</sup> Use of a second-generation or third-generation oral contraceptive is associated with 3 to 4 thromboembolic events per 10,000 woman-years—more than three times the risk in nonusers, but small in absolute numbers, considerably less than with older agents, and half the risk in pregnant women (TABLE 2).<sup>4-6</sup>

In view of this risk, oral contraceptives are still contraindicated in patients at higher risk, ie, those with any of the following:

- A history of thromboembolism
- Age greater than 35 and cigarette smoking
- A coagulation disorder. Of these, **factor V Leiden mutation** is the most common, affecting 3% to 5% of the Caucasian population. In contrast, genetic deficiencies of protein C, protein S, and antithrombin III are rare. Factor V Leiden mutation is associated with an incidence of venous thromboembolism of about 6 events per 10,000 woman-years, but taking an oral contraceptive increases the incidence to 29 events per 10,000 woman-years, suggesting that the two act synergistically to promote coagulation.<sup>5</sup>

Should all patients therefore be screened for factor V Leiden mutation before starting oral contraceptives? This step is *not* deemed necessary, since the absolute risk is still very small. However, patients should be asked about any personal or family history of

**Screening for factor V Leiden mutation is not deemed necessary for oral contraceptive users**

TABLE 2

### Incidence of venous thromboembolism with oral contraceptive use

POPULATION AND TYPE OF ORAL CONTRACEPTIVE	INCIDENCE PER 10,000 WOMAN-YEARS
Premenopausal women not taking oral contraceptives	0.8
Women taking any combined oral contraceptive	3–4
Second-generation progestins	
Monophasic levonorgestrel	2.5
Others (not levonorgestrel)	1.8
Third-generation progestins	
Desogestrel + 30 µg ethinyl estradiol	4.0
Gestodene	4.4
Pregnant women	6.0
Women with factor V Leiden mutation	
Not taking oral contraceptives	5.7
Taking oral contraceptives	28.5

venous thromboembolism, and those with a positive history should be considered for screening.<sup>7</sup>

In 1995, epidemiologic studies reported a higher risk of venous thromboembolism with the newer third-generation oral contraceptives than with the second-generation pills.<sup>8,9</sup> Subsequent studies showed that the apparent increase can be explained by discrepancies in age and age ranges used for controls, confounding factors, greater use of the older drugs in low-risk patients (ie, the “healthy user” effect), and bias due to differences in prescription practice and venous thromboembolism diagnosis.<sup>6,10,11</sup> The literature suggests that the remaining differences may not be clinically significant.<sup>10</sup> Moreover, we know of no plausible biologic basis for a higher incidence of venous thromboembolism with third-generation oral contraceptives.

**Cardiovascular disease.** Several newer studies have failed to show an increased risk of acute MI with current low doses.<sup>12–14</sup> Angiographic studies suggest that users of low-dose oral contraceptives actually have less atherosclerosis than nonusers, though no reduction in clinical coronary artery disease has been observed.

Moreover, recent studies have demonstrated that the use of second-generation and third-generation oral contraceptives does not increase the risk of stroke.<sup>10,15</sup> Smoking and increased age are the main determinants of coronary artery disease and stroke, regardless of oral contraceptive use. Current oral contraceptives do not cause hypertension, which was seen to develop in 5% of women taking high-dose (> 50 µg ethinyl estradiol) agents.

**Breast cancer.** In theory, oral contraceptives could induce or help propagate estrogen-sensitive breast cancer, although several large epidemiologic studies have not confirmed this risk.<sup>16,17</sup> In one of these studies,<sup>16</sup> women who were taking oral contraceptives did seem to have a higher incidence of early-stage breast cancer, but this finding was attributed to better detection and closer health surveillance of women taking oral contraceptives. Investigation in this area continues.

#### Progestin-related side effects

Progestin side effects such as weight gain, acne, and hirsutism are due to their androgenic properties and are far less common with the new progestins. In fact, some of the newer pills are used to *treat* some of these conditions.

#### Potential progestin side effects

**Dyslipidemia.** The third-generation oral contraceptives may have less of an adverse effect on lipid levels than older oral contraceptives. In fact, the newer agents increased HDL cholesterol levels and decreased LDL cholesterol levels and have little impact on total cholesterol levels.<sup>18</sup> The long-term implications of these changes is unknown.

**Insulin resistance.** Neither the second-generation nor third-generation progestins are associated with insulin resistance,<sup>18</sup> which was a concern in the original preparations.

**Weight gain.** A comparative study of women using oral contraceptives, depomedroxyprogesterone acetate (DMPA, Depo-Provera), and levonorgestrel implants showed no significant weight gain at 1 year, nor a statistically significant difference between the three hormonal methods.<sup>19</sup>

**Taking oral contraceptives has a lower risk of thrombosis than does pregnancy**



### Health benefits and noncontraceptive uses

Preventing pregnancy in itself has health benefits—taking oral contraceptives is much safer than pregnancy. In addition, oral contraceptives have certain noncontraceptive benefits and uses, which now account for approximately 20% of prescriptions (TABLES 3 AND 4).

Because the new third-generation progestins have no significant androgenic properties, when used in combination with low-dose estrogen they are useful in treating women with androgen-sensitive conditions such as acne, hirsutism, and polycystic ovarian syndrome. Estrogens stimulate the production of sex hormone-binding globulin, thereby reducing the level of circulating free testosterone. Concurrently, the progestin component decreases luteinizing hormone pulsatility, leading to diminished ovarian stromal production of androgens. The oral contraceptive Ortho-Tri-Cyclen is approved by the Food and Drug Administration (FDA) specifically for the treatment of acne.

Older women who do not smoke can use the low-dose (20 µg ethinyl estradiol) pills both for contraception and to treat perimenopausal menstrual irregularities.

### ■ INJECTABLE PROGESTERONE

DMPA, a synthetic progestin, was approved for contraceptive use in 1992 and is the only injectable progestin available in the United States.<sup>21</sup>

DMPA is very effective, with a failure rate of 0.3 per 100 women per year. Fertility returns once the DMPA clears from the body, which may take several months. By one analysis, 90% of women who stopped DMPA to conceive were pregnant within 24 months.<sup>22</sup>

#### Mechanism of action

DMPA prevents contraception by suppressing the luteinizing hormone surge (thereby inhibiting ovulation), inducing cervical mucus changes, and causing the endometrium to atrophy, making it unreceptive to the blastocyst. Some follicular growth may occur due to the subtotal suppression of follicle-stimulating hormone.

TABLE 3

### Noncontraceptive benefits of oral contraceptives

#### Cancer reduction

- Ovarian (risk reduced by 80% at 10 years; benefit continues for > 15 years)
- Endometrial (risk reduced by 60% at 4 years)
- Colon (possibly)

#### Gynecological benefits

- Reduced risk of:
  - Ectopic pregnancy
  - Pelvic inflammatory disease
  - Functional ovarian cysts

#### Menstrual improvements

- Reduction in:
  - Anemia
  - Premenstrual syndrome
  - Dysmenorrhea
- Restoration of regular menses

#### Other benefits

- Reduction in:
  - Benign breast disease
  - Premenopausal bone loss<sup>20</sup>
  - Acne
  - Atherosclerosis (possibly)

#### Indications

DMPA is best suited for women who desire contraception over several months to years and in whom compliance may be poor, such as adolescents and patients with mental illness.

DMPA is particularly useful after abortion. It can also be used during lactation (starting at 6 weeks postpartum) and in situations in which estrogen is contraindicated or its metabolism is altered. It can therefore be used in women with valvular heart disease, diabetes, or hypertension, and in those over age 35 who smoke.

**Contraindications** to DMPA include liver disease, breast cancer, clotting dyscrasias, and cerebrovascular disease.

**Noncontraceptive benefits** include a reduction in anemia through reduced menstrual flow, and decreased incidence of pelvic inflammatory disease and endometrial cancer. In addition, women with epilepsy have diminished seizure activity while receiving DMPA.<sup>23</sup>

**Injectable progesterone is a good option for women with poor compliance**

TABLE 4

**Newer oral contraceptives: Content and noncontraceptive uses**

PREPARATIONS	ESTROGEN DOSE	PROGESTIN DOSE	NONCONTRACEPTIVE USES
<b>Monophasic preparations</b>			
Loestrin 1/20	Ethinyl estradiol 20 µg	Norethindrone 1 mg	Ovarian cysts
Allesse	Ethinyl estradiol 20 µg	Levonorgestrel 0.1 mg	Ovarian cysts, perimenopause, use in teens
Desogen, Ortho-Cept	Ethinyl estradiol 30 µg	Desogestrel 0.15 mg	Acne, hirsutism, ovarian cysts
<b>Triphasic preparations</b>			
Ortho Tri-Cyclen	Ethinyl estradiol 35 µg	Norgestimate 0.180 mg (week 1) 0.125 mg (week 2) 0.250 mg (week 3)	Acne, hirsutism
<b>Estrophasic preparations</b>			
Estrostep 21	Ethinyl estradiol 20 µg (week 1) 30 µg (week 2) 35 µg (week 3)	Norethindrone 1 mg	Irregular menses Early cycle breakthrough bleeding
Mircette	Ethinyl estradiol 20 µg (days 1–21) 10 µg (days 22–26)	Desogestrel 0.15 mg	Midcycle bleeding Breakthrough bleeding Estrogen withdrawal headaches

**Side effects**

Overall, DMPA is safe, has few side effects (namely, irregular menses, headache, gastrointestinal upset, dizziness, and fatigue), and may also cause lower bone mineral density and dyslipidemia.

Thirty percent of women develop irregular menses and spotting during the first 3 months of DMPA therapy. Persistent bleeding can be treated by giving the next dose early or by adding an estrogen such as 1.25 mg of conjugated estrogen for 7 days. Amenorrhea develops in 50% of women at 1 year and 80% at 3 years of use.

Lower bone mineral density was observed in women who used DMPA for a minimum of 5 years than in other premenopausal women, but levels were higher than in postmenopausal controls.<sup>24,25</sup> The implication for subsequent fracture rates is unknown. Further studies are required.

Although lipid metabolism appears to be influenced adversely, these effects may be

transient and the long-term impact is unknown.<sup>21,26</sup> The effects on bone and lipids are probably due to lower circulating estradiol levels in women receiving DMPA.

There is no demonstrated increased risk of cervical, ovarian, or breast cancer with DMPA use, and there is no association with hypertension or myocardial infarction.<sup>21</sup> Studies show no link between weight gain or mood disorders and use of DMPA.<sup>26</sup>

**Dosage**

DMPA is given as a 150-mg intramuscular injection every 3 months, ideally within 5 days of onset of menstruation.

**Other preparations**

Monthly injections of an estrogen-progestin combination are in use outside the United States.<sup>27</sup> Combinations of estrogen and a progestin such as medroxyprogesterone acetate or norethindrone lead to monthly withdrawal bleeding and are very efficacious.



## ■ SUBDERMAL PROGESTIN IMPLANTS

Levonorgestrel implants (Norplant) have been available in the United States since 1990, although clinical trials were performed as early as 1972 in Chile.

Levonorgestrel implants are effective: the failure rate is 0.8 per 100 woman-years averaged over 5 years, increasing to 2 per 100 woman-years by the 6th year. Thus, after 5 years the implants should be removed. Progestin levels are negligible after removal and fertility returns immediately.

### Mechanism of action

Implantable progestins prevent conception primarily by rendering the cervical mucus impenetrable to sperm. They also inhibit ovulation and impair oocyte maturation by blocking the LH surge. However, LH blockade is inconsistent; hence, cyclic luteal activity may be seen, albeit with subphysiologic progesterone levels. Although ovulation may still occur, impaired oocyte maturation and luteal insufficiency prevent pregnancy.

### Indications

Progestin implants are best suited for women desiring long-term reversible contraception.

### Side effects

Bleeding patterns are variable due to endometrial atrophy and variable cyclic luteal activity. Amenorrhea develops in 5% to 10% of users. Irregular bleeding occurs most frequently in the first year and is usually due to endometrial atrophy. The bleeding can be treated effectively with conjugated equine estrogens 1.25 mg/day for 1 to 2 weeks.

Other side effects account for 14% of removals and include headache (most common), mood changes, local dermatitis, acne, mastalgia, and hair changes.<sup>28</sup> Functional ovarian cysts can occur but are usually asymptomatic and are treated expectantly. Levonorgestrel implants are safe to use during lactation and there has been no evidence of teratogenesis in women who conceived while on this agent. There is no clinically significant effect on glucose or lipid metabolism.<sup>29</sup> The long-term effect on cancers of the reproductive tract is not yet known.

### Dosage and administration

Six rods, each containing 36 mg of levonorgestrel in a Silastic adhesive, are inserted subcutaneously in the upper arm, ideally within 7 days of menstruation. The procedure is simple and can be performed in the office under local anesthetic. However, removal can be cumbersome due to local fibrosis.

### New preparations

Norplant-2, a two-rod version of levonorgestrel in a different elastomer, is easier to insert and remove than Norplant and is now available in the United States.<sup>30</sup> A single-rod implant (not yet available) containing the third-generation progestin desogestrel is being studied and appears very effective.<sup>31</sup> New implant systems under investigation use biodegradable materials such as cholesterol and elastomers such as poly E-caprolactone, which is easier to remove.<sup>28</sup>

## ■ PROGESTERONE-RELEASING IUD

The intrauterine device (IUD) is the most commonly used reversible method of contraception in the world.

Progesterone-releasing IUDs were developed to reduce the cramping and increased menstrual bleeding that often occur with non-medicated IUDs. However, they also have the benefit of an additional mechanism of action: Whereas nonmedicated IUDs prevent conception by producing a sterile intrauterine inflammatory response that is spermicidal, progesterone-releasing IUDs also induce decidualization of the endometrium, inhibiting implantation.<sup>32</sup>

### Indications

Progesterone-releasing IUDs are best suited for long-term contraception in parous or older women.

### Side effects

Amenorrhea or oligomenorrhea is common, due to suppression and atrophy of the endometrium. For a patient suffering from menorrhagia and anemia this may be a welcome side effect. Nevertheless 72% of all removals for menstrual irregularities were due

**Levonorgestrel IUDs last up to 7 years and should be available in the US soon**

TABLE 5

### Oral regimens for post-coital contraception

#### Estrogen-progestin (Yuzpe regimen)

Ethinyl estradiol 100 µg plus levonorgestrel 0.5 mg, repeated in 12 hours\*

#### Estrogen-progestin (Preven)

Ethinyl estradiol 50 µg plus levonorgestrel 0.25 mg, 2 pills, repeated in 12 hours

#### High-dose estrogen

Ethinyl estradiol 2.5 mg twice daily for 5 days

#### Levonorgestrel

0.75 mg repeated in 12 hours

#### Mifepristone (RU486)

600 mg single dose

\*Typically, two tablets of Ovral (50 µg ethinyl estradiol plus 0.5 mg norgestrel), or four of Lo/Ovral (30 µg ethinyl estradiol plus 0.3 mg norgestrel) are used to provide similar doses to the Yuzpe regimen; any other combined oral contraceptive may also be used

to amenorrhea.<sup>33</sup> When patients are counseled appropriately about what to expect regarding bleeding patterns, the number of IUD removals decreases.

The absolute rates of ectopic pregnancy are very low with progesterone-releasing IUDs. Ectopic pregnancy rates are higher with one type of medicated IUD (Progestasert), but lower with the levonorgestrel-containing IUD,<sup>2,34</sup> compared with rates in women who don't use contraception.

No changes in HDL-cholesterol or coagulation parameters have been observed with the progesterone-releasing IUD.<sup>35</sup>

#### Dosage and administration

Progestasert, the only hormone-releasing IUD available in the United States at present, contains 38 mg of progesterone. It must be reinserted every year.

A levonorgestrel IUD, not yet available in the United States but being evaluated for release soon, releases 20 µg of levonorgestrel per day, thereby suppressing ovulation in 55% of menstrual cycles.<sup>32</sup> The levonorgestrel IUD provides contraception for up to 7 years.<sup>2</sup>

### POSTCOITAL (EMERGENCY) CONTRACEPTION

Postcoital (emergency) contraception refers to any method used to prevent pregnancy after unprotected intercourse.

In a recent survey, only 36% of Americans had any knowledge about emergency contraception and only 1% had ever used it.<sup>36</sup> The study also showed that, although aware of its existence, very few gynecologists actually prescribe the regimen. Not until February 1997 did the FDA declare the administration of synthetic estrogen and progesterone in oral contraceptives to be an effective and safe method of emergency contraception. Guidelines from the World Health Organization state that the only absolute contraindication to this method is known pregnancy.<sup>37</sup>

Postcoital contraception can be achieved via a variety of methods: high doses of estrogen, combinations estrogen and progesterone, progestin alone, mifepristone (RU486), and IUD insertion in the immediate postcoital period (TABLE 5).<sup>37</sup>

How these agents act is not always clear; some may act at different levels. Estrogen and progestin, either alone or concurrently, act primarily by preventing or delaying ovulation.

**Combined oral contraceptives.** The most commonly used forms of emergency contraception are combined oral contraceptives. Yuzpe and Lancee<sup>38</sup> first reported the use of ethinyl estradiol and norgestrel as a postcoital contraceptive in 1977. Two doses of 100 µg of ethinyl estradiol and 0.5 mg of levonorgestrel are given 12 hours apart, within 72 hours of intercourse. The main side effects of this regimen are nausea and vomiting. Regular birth control pills that contain the same hormones are generally used, but a product specifically licensed by the FDA for emergency contraception was released in September 1998. This product, the Preven Kit, contains a urine pregnancy test to exclude pregnancy prior to taking the hormones.

**Progestin-only compounds** have been shown to be as effective as the Yuzpe regimen.<sup>39</sup> Two doses of levonorgestrel 0.75 mg

**For emergency contraception, give two doses of estradiol 100 µg plus levonorgestrel 0.5 mg, 12 hours apart**



can be given 12 hours apart, within 48 to 72 hours of unprotected intercourse. This regimen may have a lower incidence of side effects than the Yuzpe regimen.<sup>39</sup> In several countries, four tablets of 0.75 mg levonorgestrel are marketed as a postcoital contraceptive agent. Women who require postcoital contraception should be counseled and started on regular contraception.

The **copper IUD** can both diminish fertilization through a toxic effect on sperm, and impair implantation by causing changes in the endometrium.<sup>2</sup>

**Mifepristone (RU486)** is an antiprogesterone that can inhibit ovulation, but if given in the midluteal phase can cause regression of the corpus luteum in 50% of women.<sup>40</sup> When given as a single 600-mg dose, mifepristone is a very effective method of postcoital contraception. However, since it may delay endometrial maturation, the resulting delay in onset of menstruation can be anxiety-provoking for the patient, even though it effectively prevents pregnancy. Its postcoital use is separate from its use as an early abortifacient. Although widely available in Europe, mifepristone is investigational in the United States, but is being evaluated for emergency contraceptive use for approval in 2001.

## ■ MALE CONTRACEPTION

Condoms are the mainstay of male contraception. Advances include the new polyurethane condom, which is thinner, stronger, and less allergenic than the older latex condoms. While male sterilization or vasectomy is a contraceptive choice for some men, it is considered permanent. Reversible vasectomy is being investigated, whereby a polyurethane elastomer plugs the vas deferens but can be removed within 4 years.<sup>41</sup>

A variety of male contraceptives are being developed.<sup>41</sup> Hormonal methods for terminating sperm production are under investigation, but will probably not be available for another decade. An injection of an androgen and a progestin given every 3 months is under study by the World Health Organization. The androgen suppresses production of gonadotropin-releasing hormone (GnRH), reducing LH and FSH, and therefore inhibiting spermatogenesis. The progestin allows a lower dose of androgen to be used, thereby reducing side effects. Also under development are GnRH receptor antagonists that would block spermatogenesis. Because testosterone production would also decrease, androgen replacement would be required. Short-term contraceptive vaccines for men and women are also being investigated. ■

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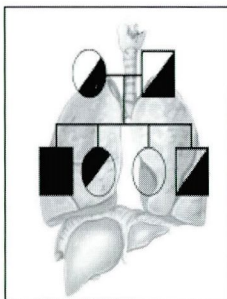
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