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Update on hormonal contraception

■ ABSTRACT

Several newer hormonal contraceptive agents have become available in recent years. Many of them are slight variations on previous agents. In this article, we review the advantages, side effects, and practical considerations of hormonal contraceptives approved in the last few years.

■ KEY POINTS

A trend in oral hormonal contraceptives is to use much lower estrogen doses than in the past, which reduces the risk of venous thromboembolism (the major risk of hormonal contraceptives) and other side effects.

In some newer regimens, women receive active hormones for 24 days per month instead of the usual 21. In other, "long-cycle" regimens, women receive active hormones for 12 weeks and then either placebo or a lower dose of ethinyl estradiol without a progestin for 1 week. Another option is a continuous regimen. With these options, women have fewer days of menstrual bleeding.

Non-oral hormonal contraceptives are available in the form of an intravaginal ring, an intrauterine device, a skin patch, a subcutaneous injection, and a subdermal implant.

Risk-benefit assessments are needed for any woman using hormonal contraceptives.

After extended political controversy, Plan B (an emergency oral hormonal contraceptive) is now available without prescription to women age 18 and older.

ALTHOUGH a variety of contraceptive options are available, the rate of unintended pregnancy in the United States remains unacceptably high. Newer hormonal contraceptive options afford women more choices and, we hope, will reduce the rate of unintended pregnancy.

Health care providers need to be informed about these newer options, as all women requesting hormonal contraceptives need an evaluation with a risk-benefit assessment before starting.

This article reviews the newest developments, including extended-cycle hormonal contraceptives and lower doses and longer intervals of existing regimens.

■ TRENDS IN HORMONAL CONTRACEPTION

Hormonal contraceptives are highly effective, reversible, and popular. They also have non-contraceptive uses, including control of menstrual abnormalities, as these agents decrease blood loss, decrease the incidence of iron-deficiency anemia, decrease dysmenorrhea, and decrease the incidence of endometrial and ovarian cancer.

"The pill" has been used for almost half a century, and well over a decade ago, the US Food and Drug Administration (FDA) reported that it was the most studied pharmaceutical agent in the history of medicine (www.fda.gov). Now, several other forms of hormonal contraceptives are available.

Some of the trends in hormonal contraception are as follows:

Lower estrogen doses. The first hormonal contraceptive agents contained high doses of estrogen and progestin. Lower doses are as effective and perhaps cause fewer side effects, such as headache, breast tenderness, nausea, and hypertension.

TABLE 1

Newer hormonal contraceptives

AGENT	ROUTE	INGREDIENTS	DURATION
Depo-subQ Provera 104	Subcutaneous	Medroxyprogesterone 104 mg	12 weeks
Femcom Fe	Oral (chewable)	Ethinyl estradiol 35 µg/ norethindrone acetate 0.4 mg Placebo	21 days 7 days
Implanon	Implantable	Etonogestrel 0.04 mg	3 years
Loestrin 24 Fe	Oral	Ethinyl estradiol 20 µg/ norethindrone acetate 1 mg Placebo (ferrous fumarate 75 mg)	24 days 4 days
Lybrel	Oral	Ethinyl estradiol 20 µg/ levonorgestrel 0.09 mg	Continuous
Mirena IUS	Intrauterine	Levonorgestrel 0.025 mg	5 years
Plan B	Oral	Levonorgestrel 0.75 mg	2 doses
Seasonique	Oral	Ethinyl estradiol 30 µg/ levonorgestrel 0.15 mg Ethinyl estradiol 10 µg	84 days 7 days
YAZ 24/4	Oral	Ethinyl estradiol 20 µg/ drospirenone 3 mg Placebo	24 days 4 days

**Hormonal
contraceptives
also have
non-
contraceptive
uses**

In particular, lower doses of ethinyl estradiol are associated with less thrombotic risk. Nowadays, contraceptive pills contain less than 50 µg of ethinyl estradiol; most contain 30 or 35 µg, and the newer ones contain 20 or 25 µg.

Newer progestins with fewer androgenic effects that are available in the United States include desogestrel and norgestimate. Although the risk of venous thromboembolism may be higher with desogestrel than with older progestins such as levonorgestrel,¹ the risk with norgestimate (and its metabolite norelgestromin, also known as levonorgestrel 3-oxime) is very similar to that with levonorgestrel.^{2,3}

Longer cycles. In some newer regimens, the patient takes placebo pills for fewer days per month than with older regimens, or the placebo pills have been replaced by low-dose hormone pills. These regimens reduce the number of days of withdrawal bleeding, with the intent of improving contraceptive effectiveness, patient adherence, and patient tolerance and reducing adverse effects. In other newer regimens, hormonal contraceptives are taken in longer cycles to lengthen the

intervals between withdrawal bleeding, or continuously, so that the patient has no bleeding at all.

Non-oral options that have been developed in an effort to improve patient adherence are vaginal rings, skin patches, injections, intrauterine devices, and implants.

Nuvaring, a 3-week vaginal ring, provides good cycle control and lower serum concentrations of hormones than do oral contraceptives.

Ortho Evra is the only transdermal hormonal contraceptive patch. Although it now carries a new FDA warning label about a risk of venous thromboembolism that is twice that with oral hormonal contraceptives, it still may be a good option for some patients (see below).

Implanon, a new subdermal implant (see below) has been recently approved in the United States and has been used in Europe, Asia, Australia, and Indonesia.

The FDA has issued updated statements regarding the use of intrauterine devices (IUDs) in nulliparous women, and we will also review all of these updates.

■ FEMCON FE: CHEWABLE TABLET

Femcon Fe, the new name for Ovcon Fe chewable, was approved by the FDA in August 2006. It has the same active ingredients as Ovcon 35, which has been available for years: ethinyl estradiol 35 µg and norethindrone 0.4 mg (TABLE 1). The difference is that the Ovcon 35 pill must be swallowed, whereas Femcon Fe is a spearmint-flavored, chewable tablet. In addition, the (chewable) placebo pill in this newer formulation contains iron (ferrous fumarate 75 mg), as many menstruating women are iron-deficient. This formulation would be advantageous to a woman who cannot swallow pills.

■ YAZ 24/4: LOWER, LONGER DOSE THAN YASMIN

Yasmin (ethinyl estradiol 30 µg and drospirenone 3 mg in a “21/7” pack, ie, 21 tablets containing active medication and 7 tablets containing placebo) has been the number-one hormonal contraceptive prescribed worldwide since its launch in 2001 (pharmaceutical sales information from Berlex).

YAZ 24/4 became available in 2006. It has the same dose of drospirenone as Yasmin (3 mg), but a lower dose of ethinyl estradiol (20 µg). In addition, the YAZ 24/4 pack contains 24 days’ worth of active medication and 4 days’ worth of placebo. Taking active hormonal pills for 24 days results in less ovarian follicular development than with the 21/7 pill packs.

Efficacy. The Pearl index, a measure of contraceptive effectiveness, is the number of pregnancies per 100 woman-years of use—if 100 women use a given method of contraception for 1 year, the Pearl index is the number of women who would get pregnant.

The contraceptive efficacy of YAZ is 99%, similar to that of other hormonal contraceptives), with a Pearl index of 0.72 after excluding women who did not adhere to the regimen.⁴

Advantages. YAZ 24/4 has an FDA indication for premenstrual dysphoric disorder (PMDD). It is the first and only hormonal contraceptive that has been shown to be effective for the treatment of the physical and emotional symptoms of PMDD.⁵

In addition, drospirenone, the progestin agent in YAZ 24/4, is a spironolactone analogue with antiandrogenic and antiminerocorticoid properties. Thus, it might benefit a woman by improving acne, hirsutism, and other skin problems. It also significantly reduces water retention and bloating.

Side effects. The most common side effects of YAZ 24/4 are similar to those of other hormonal contraceptives, eg, headache, breast pain, and vaginal candidiasis.

Practical considerations. Because drospirenone has antiminerocorticoid activity, in theory it could cause hyperkalemia, although this problem has not been reported. Nevertheless, YAZ 24/4 should not be used in patients with conditions that predispose to hyperkalemia, such as hepatic failure, renal insufficiency, and adrenal insufficiency. Moreover, women receiving medications that may increase serum potassium levels, such as angiotensin-converting enzyme inhibitors, angiotensin II-receptor antagonists, potassium-sparing diuretics (eg, spironolactone [Aldactone]), potassium supplements, aldosterone antagonists, and nonsteroidal anti-inflammatory drugs, should have their serum potassium levels checked during the first treatment cycle.

■ LOESTRIN 24 FE: LONGER DOSE THAN LOESTRIN 21/7, PLUS IRON

Loestrin 24 Fe was approved in February 2006. It provides 3 more days of the active hormonal pills than the Loestrin 21/7 pack, for a total of 24 days of active medication followed by 4 days of iron-containing placebo pills. The 24 active hormonal pills contain ethinyl estradiol 20 µg and norethindrone acetate 1 mg (the same constituents and doses as in the Loestrin 1/20 21/7 pack), and the 4 placebo pills contain ferrous fumarate 75 mg.

Advantages. With Loestrin 24 Fe, the menstrual periods are shorter (lasting less than 3 days), with less bleeding. In addition, extending the hormonal contraceptive exposure from 21 to 24 days in a 28-day regimen results in more pronounced suppression of ovarian follicular development.⁶

Side effects. The most frequent side effects of Loestrin 24 Fe include nausea, vom-

The drospirenone component in Yasmin and Yaz 24/4 is a spironolactone analogue

iting, intermenstrual bleeding, weight gain, and breast tenderness. The risks and drug interactions are considered to be the same as with any other hormonal contraceptive.

Practical considerations. With any oral contraceptive, it is important to take the pill at the same time every day to ensure a steady level of hormones. Missing a pill for more than 24 hours increases the risk of pregnancy, and the patient should be instructed to take one pill as soon as she remembers, and the next pill at the regular time. If two pills are missed, two pills have to be taken on the day the patient remembers, two pills the next day, and one pill a day thereafter.

■ SEASONIQUE: FOUR CYCLES PER YEAR

Long-cycle hormonal contraceptives reduce the number of withdrawal menses periods from one per month to four per year. Seasonale (ethinyl estradiol 30 µg and levonorgestrel 0.15 mg) is a long-cycle oral contraceptive that has been available since 2003: patients receive active treatment for 12 weeks followed by placebo for 1 week, which is the week for scheduled bleeding.

Seasonique, which was approved in May 2006, is the same formulation as Seasonale but with the addition of ethinyl estradiol in a lower dose (10 µg) during the 13th week, without levonorgestrel.

Effectiveness. In a 1-year, multicenter, open-label study,⁷ Seasonique was more than 99% effective in preventing pregnancy when taken as directed, with a method failure rate (Pearl index) of 0.78. Cycle control and safety of the regimen were similar to those reported for other hormonal contraceptives.

Advantages. Some women may choose long-cycle hormonal contraceptives for lifestyle and cosmetic reasons, ie, to have fewer periods. Symptoms related to hormone withdrawal, such as headache and dysmenorrhea, are reduced with this extended-cycle oral contraceptive, as the number of withdrawal bleeding periods are reduced to four per year as opposed to 13.

The addition of low-dose ethinyl estradiol during the 13th week with Seasonique may reduce the hormonal withdrawal symptoms

such as menstrual migraine and dysmenorrhea that may occur during the placebo week with long-cycle hormonal contraceptives.

Further, continuous exposure to progestin (as with some other hormonal contraceptives) can lead to endometrial atrophy and breakthrough bleeding. The low dose of estrogen during the withdrawal period with Seasonique may stabilize an atrophic endometrium, thereby causing less breakthrough bleeding than with other long-cycle continuous hormonal contraceptives.

Side effects. Women on continuous long-cycle hormonal contraceptives tend to have more unscheduled bleeding than do women on shorter-cycle regimens, although such bleeding tends to decrease over time. In the main clinical trial of Seasonique, 82 of 1,006 women quit taking it, at least partly because of bleeding. The other reported adverse events were nasopharyngitis, sinusitis, and unscheduled bleeding.

■ LYBREL: A NONCYCLING REGIMEN

Lybrel, a low-dose oral contraceptive, contains ethinyl estradiol 20 µg and levonorgestrel 0.09 mg. What is unique about it is that it is taken in a continuous, noncyclic, 365-day regimen.

The FDA issued a letter in June 2006 asking for more data on Lybrel; as of this writing, it has not yet been approved.

Advantages. There is no hormone-free period with this regimen. Therefore, hormone levels remain constant, ovulation is suppressed, and women have no menstrual bleeding.

Disadvantages. For women with hemochromatosis, not having a period might be a disadvantage: women with hemochromatosis who have regular monthly bleeding lose enough iron so that they present much later than do women who do not have monthly bleeding. This appears to be the only advantage of regular menstrual bleeding.

■ INTRAUTERINE DEVICES: SAFE, EFFECTIVE, UNDERUSED

Intrauterine devices (IUDs) fell out of favor in the United States after one IUD, the Dalkon Shield, was linked to severe pelvic inflamma-

For women with hemochromatosis, regular menstrual bleeding may be a good thing

tory disease, infertility, and death. The Dalkon Shield was recalled in 1975 and is no longer used in the United States.⁸ For these reasons, IUDs have traditionally been recommended for women in monogamous relationships, with at least one child, and without a history of pelvic inflammatory disease. Nevertheless, studies have proven that current IUDs are safe, effective, and underused in the United States.⁹

ParaGard: A hormone-free copper IUD has an expanded indication

ParaGard is a hormone-free copper IUD that has been approved for contraceptive use since 1984. It is 99% effective in preventing unplanned pregnancy.

In December 2005, the FDA approved ParaGard for women in all stages of reproductive life who are in a stable relationship. It is also approved for women with a history of sexually transmitted diseases or pelvic inflammatory diseases and in nulliparous women. However, women with acute pelvic inflammatory disease or those engaging in high-risk sexual behaviors should not use an IUD.

Once inserted, ParaGard provides birth control for as long as 10 years. The most common side effects are heavier and longer periods with spotting. These symptoms generally improve within a year of insertion.

Practical considerations. To make sure that the IUD has not been expelled during menstruation, the patient should be instructed to insert a finger into the vagina once a month after her period is over to check that the threads are still protruding from the cervix. The physician needs to be notified if the threads are not felt.

IUDs do not protect against sexually transmitted infections.

Mirena IUS: A progestin-releasing IUD

Mirena IUS, a T-shaped IUD (“IUS” stands for “intrauterine system”), was approved by the FDA for long-term contraception (up to 5 years) in 2000, although it has been used in Europe since the 1980s. Measuring 32 mm both horizontally and vertically, it contains 52 mg of levonorgestrel and releases 25 µg per day. It is inserted within 7 days of the onset of the menstrual period.

Efficacy. Mirena is 99.9% effective in preventing pregnancy.¹⁰

Advantages. Placement of the Mirena device is a simple office procedure with no need for anesthesia, although the technique is slightly different than with the ParaGard IUD. The duration and severity of blood loss during menses are markedly decreased. The Mirena device also may decrease menorrhagia and can be considered for off-label use for dysmenorrhea, endometriosis, and menorrhagia if the patient has a negative workup for abnormal bleeding.

Side effects. Most of Mirena’s side effects, eg, spotting and bleeding, are seen within the first 6 months after insertion. After 6 months, the side effect profile improves, with less bleeding, and about 20% of women have amenorrhea by the end of the first year.¹¹ The risk of pelvic infection also decreases after the first month after insertion.

■ SUBCUTANEOUS DEPO-PROVERA

Depo-subQ Provera 104, a subcutaneous version of the intramuscular Depo-Provera shot, was approved in 2004. It contains medroxyprogesterone 104 mg, compared with 150 mg in the intramuscular version. Like Depo-Provera, it is given every 12 to 14 weeks.

Advantages. The subcutaneous version is as effective as the intramuscular version in preventing pregnancy. It may be effective in treating pain related to endometriosis.^{11,12} There is no need to adjust the dosage on the basis of weight, and subcutaneous injections are less painful than intramuscular injections. Depo-subQ Provera 104 comes in prefilled syringes, so either the clinician can give the injection, or the patient can give herself the injection in the thigh or abdomen every 12 to 14 weeks in the comfort of her home without needing to go to the clinic. This convenience may improve adherence.

Side effects. The subcutaneous formulation has a side effect profile similar to that of the intramuscular formulation, including irregular bleeding and delayed fertility up to 10 months after stopping the shots.

It also causes short-term loss of bone mineral density due to estrogen suppression. Bone loss is greater the longer it is used.

Irregular bleeding is more common with continuous progestin exposure

Since 2004, the FDA has required a controversial black-box warning that Depo-Provera should not be used long-term. It can be used for longer than 2 years only if other birth control methods are inadequate, with consideration of bone mineral density testing with dual-energy x-ray absorptiometry. Depo-Provera has not been specifically linked to menopausal osteoporosis or fractures,¹² and some data show that the decline in bone mineral density is not permanent. Cundy et al¹³ in New Zealand found that patients lose bone mineral density while using the subcutaneous formulation, but they recover it after the medication is discontinued. In addition, cross-sectional data from the World Health Organization showed that former users had bone mineral densities similar to those in never-users.¹⁴ Further study is needed with fracture outcomes.

■ IMPLANON: A SINGLE-ROD IMPLANT

Implanon, the first single-rod implantable contraceptive, was approved in July 2006 and became available in August 2006. This 4-cm by 2-mm rod, made of a soft flexible polymer, is placed subdermally in the medial aspect of the nondominant arm. It contains 68 mg of etonogestrel, which is a metabolite of desogestrel (a newer progestin), and it releases approximately 40 µg of etonogestrel daily. This synthetic progestin has the dual action of inhibiting the luteinizing hormone surge in the pituitary, thus suppressing ovulation, and reducing sperm penetration by increasing the thickness of the cervical mucus.

Efficacy. Implanon provides effective contraception for up to 3 years. It was actually 100% effective in preventing pregnancy in clinical trials, but it is listed as only 99% effective because some of the women got pregnant after the implant was removed, and the FDA requires that all pregnancies that occur within 2 weeks of discontinuation be counted. On the positive side, these pregnancies show that the contraceptive effect of Implanon is readily reversible. The Pearl index is less than 0.07 pregnancies per 100 woman-years, provided that the device is implanted in the first 5 days of the menstrual cycle.

Advantages. Implanon is very convenient and frees women from thinking about birth

control for 3 years once placed. The contraceptive effect is highly and rapidly reversible. Blood levels of etonogestrel fall within a week after removal; hence, most women begin ovulating again within 1 month. (In contrast, with Depo-Provera, ovulation can take longer to resume.) Implanon has not been reported to affect bone density, but further study is needed, as it is a progestin (non-estrogen) hormonal contraceptive. Since there is no estrogen in Implanon, it would be expected to pose a lower risk of venous thromboembolism. Implanon is much easier to insert and remove than Norplant was: Implanon is only one rod, whereas Norplant was six. (Norplant is no longer available in the United States.)

Side effects. As Implanon contains no estrogen, its common side effects include spotting, irregular bleeding, and amenorrhea (all linked to endometrial atrophy). Fluid retention, weight gain, and breast tenderness are less-common side effects. Local complications of implantation include swelling, redness, pain, and hematoma formation.

Practical considerations. Correct insertion technique and timing of insertion play major roles in the effectiveness of Implanon. The FDA has mandated that providers undergo special training to place or remove Implanon (though this is a simple procedure done under local anesthesia), and the manufacturer will not allow physicians to order Implanon before they are trained. Removal of Implanon requires a small (2- to 3-mm) incision. We expect that Implanon will be much easier to insert and remove than Norplant was.

Timing of insertion is very important to avoid failures: ideally, Implanon should be inserted between day 1 and day 5 of the menstrual cycle. If done during other days of the menstrual cycle, a pregnancy test must be done to be sure that the patient is not pregnant. Also, the patient should be advised to use another method of contraception for at least 1 week after insertion.

■ PLAN B: NOW WITHOUT A PRESCRIPTION

Plan B (the “morning-after pill”) has been available for emergency contraception by prescription since 1999. However, in August 2006, after lengthy political maneuverings

Plan B users younger than 18 still need a prescription for it

and controversy, it was approved for behind-the-shelf sales by pharmacists to women age 18 and older presenting photo identification.

Plan B contains two pills, each containing 0.75 mg of levonorgestrel. The first pill needs to be taken within 72 hours of unprotected intercourse, and the second one 12 hours later. However, the levonorgestrel dose does not really have to be split: studies have shown that a single 1.5-mg dose of levonorgestrel within 72 hours of unprotected intercourse is just as effective as the split dose.¹⁵

Plan B is an emergency hormonal contraceptive, not an abortive agent, and it will not work if a woman is already pregnant.¹¹ Its efficacy and safety have been demonstrated in women and girls age 13 and older. Emergency hormonal contraception has been underutilized and underrecognized, and we hope that removing the prescription barriers, at least for postadolescent women, will reduce unintended pregnancies. Studies show that Plan B, if taken properly (within 3 days of unprotected intercourse), reduces the rate of unintended pregnancy by 89%.

■ NEW LABELING INFORMATION FOR THE ORTHO EVRA PATCH

Ortho Evra, the first and only transdermal contraceptive patch, was approved in 2001. It delivers ethinyl estradiol 20 µg and norelgestromin (a metabolite of the newer progestin norgestimate) 150 µg per day. The patch is applied once a week for 3 weeks, followed by a patch-free week.

In November 2005, the FDA approved updated labeling on this patch. The patch exposes women to higher levels of estrogen than most oral hormonal contraceptives pills, and in September 2006 the FDA added new warnings that users could have twice the risk of blood clots than users of oral hormonal contraceptives due to higher levels of estrogen exposure (although it is not definite that the risk is higher).

In a study of ethinyl estradiol pharmacokinetics, Van den Heuvel et al¹⁶ found that women using the Ortho Evra patch were exposed to a concentration of ethinyl estradiol that was 3.4 times higher than in women using the NuvaRing and 1.6 times higher than

in women on oral contraceptives containing ethinyl estradiol 35 µg. With oral contraceptives, hormone levels reach a peak after the patient takes the pill, then decline throughout the day. With the transdermal patch, serum hormone levels are 25% lower than the peak with oral contraceptives but they are steady throughout the day. Over 24 hours, women wearing the Ortho Evra patch are exposed on average to 60% more estrogen in the blood than women on oral hormonal contraceptives containing 35 µg of estrogen.

The biggest risk of any hormonal contraceptive therapy is thrombosis. With oral hormonal contraceptives, thrombosis has been estimated to occur in 2 to 5 per 10,000 women; with patch hormonal contraceptives, the risk is estimated at perhaps 4 to 8 per 10,000.

It is unclear whether women using Ortho Evra will have an absolute increase in deep venous thrombosis related to the higher estrogen level or whether this is also related to the norelgestromin component. Ortho-Evra remains on the market and may be a good option for women who have difficulty adhering to other hormonal contraceptive regimens.¹⁷

■ THE TODAY SPONGE IS BACK

The Today sponge, a nonhormonal contraceptive spermicidal sponge that was available in the 1980s and 1990s but was taken off the market due to manufacturing issues, is now back on the market, available for over-the-counter purchase.

Efficacy. The effectiveness of the Today sponge when used appropriately and consistently is 89% to 91%.

Advantages. This is a nonhormonal contraceptive and lacks hormonal side effects. It is available over-the-counter and is to be used only when needed. It requires no special fitting, becomes effective immediately after insertion, and protects against pregnancy for the next 24 hours without the need of additional spermicide. It mimics the feel of vaginal tissue and is therefore not detected by partners.

Practical considerations. The Today sponge should be kept in place for 6 hours after intercourse to assure effective contraception. However, it should not be left in place for more the 30 hours after insertion. ■

The biggest risk of any hormonal contraceptive is thromboembolism



Liver Disease in Women Summit



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- Outline specific health-related issues for women with liver disease.
- Define key management and counseling issues regarding prevention, containment, and transmission of liver disease in women, especially as they pertain to sexuality issues.
- Identify optimal treatment strategies for liver disease and related complications in women.
- Establish a relevant research agenda for liver disease in women.

Keynote Presentation:

Is Women's Health Neglected in Liver Disease?

Teresa Wright, MD, University of California, San Francisco

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CME ANSWERS

Answers to the credit test on page 239 of this issue

1 E 2 C 3 A 4 A 5 C 6 A 7 A 8 E 9 B 10 E 11 B 12 B