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CONTRACEPTION

- New routes, new regimens
- Array of options for emergency contraception

Clip-and-save chart, page 46

- The IUD makes a comeback
- Does body weight limit contraceptive efficacy?

It's surprising to realize that the birth control pill, which launched a revolution in women's sexuality and health, has been around for less than 50 years—especially considering the myriad of methods and products on the market today. New types of contraceptives have become available, more are on the way, and noncontraceptive benefits continue to accrue. This article reviews noteworthy changes and upcoming products.

Continuous contraception: New routes, new regimens

When it was introduced in 1960, the oral contraceptive (OC) consisted of 20 or 21 active pills followed by a pill-free interval of 7 or 8 days. No medical reason justified the pill-free interval; it was devised simply to trigger menses and reassure the woman she was not pregnant.

That pill-free interval shrank as we gained awareness of the benefits of continuous OC regimens, particularly in the treatment of endometriosis. Advantages—well documented by Sulak[1]—include marked reduction or elimination of menses-related symptoms such as menorrhagia, dysmenorrhea, and menstrual migraines.

Continuous OCs became "official" in 2003 with the introduction of Seasonale (ethinyl estradiol, 0.03 mg/levonorgestrel, 0.15 mg), a continuous regimen taken for 84 days, followed by a 7-day pill-free interval.[2]

This regimen reduces the number of periods to 4 each year.

Breakthrough bleeding diminishes over time. Although breakthrough bleeding is a common side effect of continuous oral contraception—as it is with conventional regimens—it decreases with each successive cycle of Seasonale. By the fourth cycle, it is comparable to the level reported by women on a conventional regimen. Prolonged and heavy bleeding also can be managed by discontinuing pills for 7 days.

Other methods also can be used continuously. Continuous contraception is not limited to oral contraception.

The contraceptive ring (Nuvaring; ethinyl estradiol/etonogestrel) can be left in place for 4 weeks instead of 3 without decreasing efficacy. Both hormone levels are sufficient to prevent pregnancy throughout these weeks.[3]

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Emergency contraception protocols

All oral contraceptive doses are given twice, 12 hours apart

CONTRACEPTIVE	FORMULATION	PILLS PER DOSE	SUCCESS RATE*
ORAL PROGESTIN			**88%**
Plan B	0.75 mg levonorgestrel †	1	
Plan B equivalent Ovrette	0.075 mg norgestrel	20	
COMBINATION ORAL CONTRACEPTIVES (YUZPE)			**75%**
Preven	0.25 mg levonorgestrel 0.05 mg ethinyl estradiol (EE)	2	
OC formulations ‡ Ovral	0.5 mg norgestrel 50 mcg EE	2	
Alesse or Levlite	0.1 mg levonorgestrel 20 mcg EE	5	
Nordette or Levlen	0.15 mg levonorgestrel 30 mcg EE	4	
Lo/Ovral	0.3 mg norgestrel 30 mcg EE	4	
Triphasil or Tri-Levlen	0.05 or 0.125 mg levonorgestrel 30 mcg EE	First 4 or last 4	
COPPER IUD			**99%**
Paraguard			

* If 100 women had unprotected intercourse once during the 2nd or 3rd week of their cycle, about 8 would become pregnant; after treatment with emergency contraceptive protocols, 2 would become pregnant, a 75% reduction.

† A single dose totalling 1.5 mg levonorgestrel has been shown to be as effective as the 2-dose regimen, and to cause similar side effects.

‡ Combinations of oral contraceptives can be substituted for 2 Ovral tablets, and may be more readily available. Formulations should total at least 100 µg ethinyl estradiol/1000 µg norgestrel or 100 µg ethinyl estradiol/500 µg levonorgestrel

Nor is there any reason to doubt the efficacy of continuous use of the contraceptive patch (Evra; ethinyl estradiol/norelgestromin).

New regimens. A regimen of 24 active pills and a 4-day pill-free interval is available in Europe. The shorter pill-free interval allows further reduction of the active components ethinyl estradiol and gestadene. This agent contains 15 µg estradiol per pill.[4]

A version of Yasmin that contains only 20 µg of ethinyl estradiol, should be released in the United States later this year. It will consist of 24 active pills and a 4-day pill-free interval.

New implantable rod. Implanon, a new single-rod contraceptive implant containing etonogestrel, is available outside the United States and may become available here in the near future.[5,6] It can be inserted in 1.6 minutes, removed in 2.6 minutes, and lasts 3 years. No pregnancies were reported in clinical trials.

Lower dose of Depo-Provera effective for 3 months. A new dose and route of administration for Depo-Provera (depot-medroxyprogesterone acetate) is just as effective as the 150-mg intramuscular dose.

The new dose is 104 mg administered

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subcutaneously every 3 months. When it becomes available in the near future, this preparation should allow women to administer the drug at home.[7]

Emergency contraception: A variety of methods, but still need a prescription

The different methods of emergency contraception are listed in a clip-and-save chart on page 46, which can be photocopied for convenient reference.

Trussell and colleagues'[8] excellent review prefers the term *emergency contraception* to refer to contraceptive use after intercourse has occurred. The term "morning-after pill" is confusing because the method can be used any time after intercourse for up to 72 hours. It can even be used after 72 hours, albeit at reduced efficacy.

The Yuzpe regimen is the oldest and probably most popular form of contraception. It involves taking 2 Ovral tablets (ethinyl estradiol/levonorgestrel) followed by 2 more tablets 12 hours later. Each dose consists of 100 μg of estradiol and 0.5 mg of norgestrel.

Unfortunately, Ovral is not readily available in pharmacies. An alternative is taking enough OCs to equal the 100-μg dose of ethinyl estradiol and the 0.5 mg dose of norgestrel. For example, 5 tablets of Alesse or Levlite can be substituted for the 2 Ovral.

Efficacy is 75%. That is, if 100 women have unprotected intercourse once during the second or third week of their cycle, about 8 will become pregnant without treatment, and only 2 will become pregnant after treatment—a 75% reduction.

OCs that contain different progestins have not been studied extensively. They appear to work with lower efficacy than pills containing levonorgestrel.

- **Common side effects** include nausea and vomiting. Co-administration of an anti-nausea agent may be necessary. About 50% of women experience nausea and 20% vomit within 2 hours of taking a dose; some clinicians recommend repeating that dose to assure efficacy. One option is giving two 25-mg tablets of the over-the-counter drug meclizine 1 hour before combined emergency contraceptive pills; this reduces the risk of nausea by 27% and vomiting by 64%, but the risk of drowsiness doubles. Taking the medicine with a meal does not lower the rate of nausea.
- **Contraindications.** The only contraindication is an established pregnancy, since the drugs are taken so briefly.

Plan B Consists of 0.75 mg levonorgestrel taken within 72 hours of intercourse, followed by a second dose 12 hours later. This regimen has fewer side effects than the Yuzpe plan and may be slightly more effective. Unfortunately, the US Food and Drug Administration failed to approve over-the-counter status for this drug, so a prescription is still necessary.

IUDs. Insertion of a copper IUD (Paraguard)—but not a levonorgestrel-containing device (Mirena)—within 72 hours after intercourse is almost completely effective in preventing pregnancy. It also provides continuing contraception. Its mechanism of action is preventing implantation of a fertilized egg. Mirena has no efficacy in this regard.

"Every Woman, Every Visit," the American College of Obstetricians and Gynecologists' public education campaign, urges Ob/Gyns to provide advance prescriptions for emergency contraception at every office visit.

The IUD makes a comeback

After many years of declining choices in the realm of intrauterine devices (IUDs), the Mirena levonorgestrel-containing system was released in the US market in 2000. Like the Paraguard copper IUD, the Mirena prevents pregnancy at a rate equivalent to tubal ligation. These devices last for 5 and 10 years, respectively.[9,10]

In the United States, interest in IUDs declined after they were associated with salpingitis and tubo-ovarian abscess. More recent epidemiological evidence indicates that IUDs

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do not increase the risk of infection over the general population, but the rate is higher than with other forms of contraception, which offer some protection against salpingitis. Antibiotic prophylaxis is not necessary.

The removal rate for pelvic inflammatory disease is much lower for Mirena than for the copper IUD and may be related to the low levels of levonorgestrel, which thicken cervical mucus and prevent sperm transport.[9]

Ectopic pregnancy rates with the Mirena are about 1/8 to 1/10 those observed in the general population. Once the Mirena device is removed, fertility returns rapidly[9-11]

Recommended for the chronically ill. According to the World Health Organization, IUDs are the safest form of contraception for medically complicated patients.[12] Certainly, they are underutilized in this circumstance.

Noncontraceptive benefits. Slow release of low doses of levonorgestrel by Mirena reduces endometrial thickness and menstrual blood loss.[13] In fact, several studies have found the Mirena to be equivalent to endometrial ablation.[14] In a randomized study, two thirds of the women scheduled for hysterectomy for abnormal uterine bleeding cancelled surgery due to satisfaction with Mirena's bleeding profile.[15]

Ovarian cancer also is reduced.[16]

Does obesity limit contraceptive efficacy?

Decreased efficacy of the contraceptive patch, observed in overweight women,[17] especially those heavier than 198 lb, prompted reevaluation of other forms. In a retrospective analysis, Holt and colleagues[18] found a higher pregnancy rate in women heavier than 155 lb as the estrogen dose decreased. In contrast, no pregnancies occurred in women weighing more than 198 lb in a randomized trial[2] of 30 μg ethinyl estradiol/150 μg levonorgestrel (Seasonale). It is unclear why Holt failed to analyze progestin content, since it is the progestin that inhibits ovulation and prevents pregnancy.

Unfortunately, few clinical trials involve obese women. For example, the contraceptive ring was not evaluated in obese women.

Despite this shortcoming, I have not changed my prescribing of contraceptives in obese women, but await better, more convincing data. Until then, it seems wise to include a broad range of body weights in future trials. ■

REFERENCES

1. Sulak PJ, Kuehl TJ, Ortiz M, Shull BL. Acceptance of altering the standard 21-day/7-day oral contraceptive regimen to delay menses and reduce hormone withdrawal symptoms. *Am J Obstet Gynecol*. 2002;186:1142–1149.
2. Anderson FD, Hait H. A multicenter, randomized study of an extended cycle oral contraceptive. *Contraception*. 2003;68:89–96.
3. Timmer CJ, Mulders TM. Pharmacokinetics of etonogestrel and ethinyl estradiol released from a combined contraceptive vaginal ring. *Clin Pharmacokinetics*. 2000;39:233–242.
4. Sullivan H, Furniss H, Spona J, Elstein M. Effect of 21 day and 24 day oral contraceptive regimens containing gestodene (60 μg) and ethinyl estradiol (15 μg) on ovarian activity. *Fertil Steril*. 1999;72:115–120.
5. Croxatto HB, Urbancsek J, Massai R, Coelingh BH, van Beek A. A multicentre efficacy and safety study of the single contraceptive implant Implanon. Implanon Study Group. *Hum Reprod*. 1999;14:976–981.
6. Zheng SR, Zheng HM, Qian SZ, Sang GW, Kaper RF. A randomized multicenter study comparing the efficacy and bleeding pattern of a single-rod (Implanon) and a six-capsule (Norplant) hormonal contraceptive implant. *Contraception*. 1999;60:1–8.
7. Jain J, Dutton C, Nicosia A, Wajszczuk C, Dode FR, Mishell DR. Pharmacokinetics, ovulation suppression and return to ovulation following a lower dose subcutaneous formulation of Depo-Provera. *Contraception*. 2004; 70, 11-18.
8. Trussell J, Ellertson C, Stewart F, Raymond EG, Shochet T. The role of emergency contraception. *Am J Obstet Gynecol*. 2004;190:S30-S38.
9. Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. *Contraception*. 1994;49:56–72.
10. Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussell J. The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization [see comment]. *Am J Obstet Gynecol*. 1996;174:1161–1168.
11. Andersson K, Batar I, Rybo G. Return to fertility after removal of a levonorgestrel-releasing intrauterine device and Nova-T. *Contraception*. 1992;46:575–584.
12. World Health Organization. *Improving Access to Quality Care in Family Planning: Medical Eligibility Criteria for Contraceptive Use*. Geneva: WHO; 2000.
13. Milsom I, Andersson K, Andersch B, Rybo G. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *Am J Obstet Gynecol*. 1991;164:879–883.
14. Crosignani PG, Vercellini P, Mosconi P, Oldani S, Cortesi I, De Giorgi O. Levonorgestrel-releasing intrauterine device versus hysteroscopic endometrial resection in the treatment of dysfunctional uterine bleeding. *Obstet Gynecol*. 1997;90:257–263.
15. Lahteenmaki P, Haukkamaa M, Puolakka J, et al. Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy [see comment]. *BMJ*. 1998;316:1122–1126.
16. Ness RB, Grisso JA, Vergona R, et al. Oral contraceptives, other methods of contraception, and risk reduction for ovarian cancer [see comment]. *Epidemiology*. 2001;12:307–312.
17. Zieman M, Guillebaud J, Weisberg E, Shangold GA, Fisher AC, Creasy GW. Contraceptive efficacy and cycle control with the Ortho Evra/Evra transdermal system: the analysis of pooled data. *Fertil Steril*. 2002;77:S13–S18.
18. Holt VL, Cushing-Haugen KL, Daling JR. Body weight and risk of oral contraceptive failure. *Obstet Gynecol*. 2002;99:820–827.

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