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Combination Hormonal Contraception Options Reviewed

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New contraceptive options are emerging. For many women in the US, combined oral contraceptives (COCs) are the method-of-choice due to their extensive safety profile, non-contraceptive benefits, and ease of use over barrier methods. However, COCs are limited by problems with compliance and user failure. Despite the availability of counseling and education, many women are still not consistent users of birth control. With perfect use under clinical conditions, the lowest expected failure of COCs is less than 0.1% in the first year of use (1). Under nonclinical (i.e. "real-world") conditions failure rates are closer to 5%. Studies suggest that 20-30% of women miss a pill per month, and adolescents miss an average of 3 pills per month (2).

Other factors make COCs less than ideal for many women. Adverse effects attributable to either the estrogen or progestin component of COCs such as nausea, headache, breakthrough bleeding and/or spotting, breast tenderness, weight gain and bloating often contribute to premature discontinuation and decreased patient satisfaction. Results of a decision-tree analysis following COC users over one year suggest that over 1 million unintended pregnancies are related to COC use, misuse or discontinuation (3).

Thus, alternatives to oral COCs are being evaluated and developed in attempt to improve compliance and satisfaction and/or reduce adverse effects. Recently, two alternative delivery systems of combined hormonal contraception have been approved for use -- a vaginal ring, NuvaRing and a transdermal patch, Ortho Evra. Comparisons of contraceptive efficacy represented by the Pearl Index (number of pregnancies per 100 person-years of exposure) and adverse effects to COCs are provided when available.

NUVARING (ETONOGESTREL / ETHINYL ESTRADIOL)

NuvaRing, approved in October 2001, is a flexible, transparent contraceptive vaginal ring. The ring is approximately 2 inches in diameter and releases 15 mcg/day ethinyl estradiol and 120 mcg/day etonogestrel (the active metabolite of desogestrel, a progestin present in several third generation oral contraceptives) (4). NuvaRing is inserted into the vagina by the patient where it is to remain continuously for 3 weeks. The ring is then removed on week 4 for a one-week, ring-free period during which a withdrawal bleed typically ensues. A new ring is inserted one week later. If desired, the ring may be removed for up to 3 hours during vaginal intercourse; however, if removed or expelled for > 3 hours, contraceptive effectiveness may be reduced, a new ring must be inserted, and a backup method of contraception should be used for 7 days. Its drug interaction profile is expected to be similar to combined oral contraceptives. Likewise, the efficacy of NuvaRing appears comparable to combined oral contraceptives. In clinical trials of 13 cycles of use, the Pearl Index was 0.65 to 1.18.

In two one-year, open-label, noncomparative studies, contraceptive efficacy, cycle control, tolerability, and patient acceptance were evaluated in 2,322 women aged 18-40 years on an intent-to-treat basis (5). A new vaginal ring was inserted for each 28-day cycle of use over 13 cycles. Over 35% of subjects (n=821) discontinued treatment prematurely. Of those, 18.5% discontinued for nonmedical or nondevice-related reasons, including no further need for contraception and loss to follow-up. In the intent-to-treat population, 85.6% of cycles were considered compliant with the dosing regimen according to subject diaries. A total of 21 pregnancies occurred throughout the study period, resulting in a Pearl Index of 1.18 (95% CI 0.73, 1.80). Eleven pregnancies occurred in women who reported noncompliance (extended ring-free period, two or more consecutive days without ring use during a ring-use period, or a misunderstanding of how to use the ring). Withdrawal bleeding occurred in 98.5% of cycles; the median day of onset was 3 days after ring removal and the mean duration was 4.5 to 5.2 days. In 23.9% of cycles, withdrawal bleeding (most often spotting) continued into the next cycle of treatment. The incidence of breakthrough bleeding and/or spotting and subsequent treatment withdrawals were low, with an average of 5.5% per cycle and 0.8% overall. In clinical studies rates of intermenstrual bleeding have been reported to be approximately 0-12% (6). Over 65% of NuvaRing users reported at least one adverse event, with 15.1% discontinuing treatment due to an adverse event. Headache (5.8%), vaginitis (5.6%), leukorrhea (4.8%), and device-related events (4.4%) were most common. Device-related events included foreign body sensation; accidental expulsion due to improper insertion, upon removing a tampon, or straining while moving the bowels; and coital problems. Adverse effects typical of oral contraceptives such as acne, breast tenderness, weight gain, and nausea ranged from 2-4%. Of the adverse events leading to study withdrawal, device-related events (2.5%) were the most common. Subject acceptance of the ring was 85% at the end of the study.

The tolerability of NuvaRing was further compared to a combined oral contraceptive containing ethinyl estradiol 30 mcg and levonorgestrel 150 mcg for 6 cycles in 247 women in 3 small, similarly designed studies (7). Compliance was high among both groups (92.4% with NuvaRing and 75.4% with the COC). The incidence of irregular bleeding was ≤ 5% and 5.4-38.8% in NuvaRing and oral contraceptive users respectively. In addition, NuvaRing was associated with a higher incidence of a normal intended bleeding pattern ($p<.01$). Overall, the percentage of reported adverse effects was similar (Table 1); however, more women in the NuvaRing group (9.9%) discontinued the study because of adverse effects than women in the COC group (3.2%).

Table 1: Adverse Effects of NuvaRing and COC (7)

Adverse Effect	NuvaRing % (n=121)	COC % (n=126)
Acne	1.7 (2)	2.4 (3)
Decreased libido	8.3 (10)	0
Breast tenderness	4.1 (5)	4 (5)
Nausea	5 (6)	3.2 (4)
Vaginitis	4.1 (5)	1.6 (2)
Headache	3.3 (4)	2.4 (3)
Weight gain	3.3 (4)	1.6 (2)
Device-related	2.5 (3)	NA

In summary, NuvaRing offers an alternative method of administration to combined oral contraceptives with a similar efficacy profile. The pregnancy rate of 1-2% in a clinical trial setting is similar to traditional COCs. Its primary advantage is that it avoids daily administration requirements of COCs. Disadvantages include a lack of safety data beyond 13 cycles of use and the unresolved risk of accidental expulsion, which led to treatment discontinuation in close to 3% of women in clinical studies (7). Expulsion may occur with improper insertion, tampon use or straining during bowel movement. If expulsion occurs, the ring can be rinsed with water and reinserted; however, if out for >3 hours, a new ring must be inserted and backup contraception is required for 7 days. Additionally, the ring should not be used in women with vaginal stenosis, cervical prolapse, rectoceles, and cystoceles.

ORTHO EVRA (NORELGESTROMIN / ETHINYL ESTRADIOL)

Ortho Evra, a combination transdermal contraceptive patch, was approved in November 2001, and provides continuous levels of norelgestromin (150 mcg/day) and ethinyl estradiol (20 mcg/day) (8). Norelgestromin is the active metabolite of norgestimate, the progestin present in Ortho Cyclen and Ortho Tri-Cyclen. The patch is applied once weekly on the same day for 3 weeks, followed by a "patch-free" week during which a withdrawal bleed is expected. If the patch is not replaced within 48 hours of the scheduled replacement, a new 4-week cycle and backup contraception for 7 days is recommended. The patch is applied to the abdomen, upper arm, buttocks or torso (excluding the breast) and may be worn during swimming, bathing and exercising. Patches that are no longer adherent should be replaced. The use of adhesives or wraps is not recommended.

In a comparative trial, 1,147 healthy women aged 18-45 years were randomized to Ortho Evra (n=812) or Triphasil (n=605) for a treatment period of 6-13 cycles (9). The overall Pearl Indices (1.24 for OrthoEvra and 2.18 for Triphasil) were not significantly different. Compared to Triphasil, the incidence of breakthrough bleeding and/or spotting with the patch was significantly higher in the first 2 cycles, however they were similar during subsequent cycles. Breast discomfort (18.7% vs. 5.8%) and dysmenorrhea (13.3% vs. 9.6%) were also more common with the patch. User compliance was greater with the patch (88.2% vs. 77.7%; p< .001). The patch detachment rate was 1.8%. Also of note, increases in total cholesterol and triglyceride levels were significantly higher in patch users. The clinical significance is unknown. Overall, the withdrawal rate was higher with the patch group than in the COC group (22.0% vs. 12.1%, P<0.0001).

In a pooled analysis of 3 studies involving 3,319 women who completed 22,155 cycles of norelgestromin/ethinyl estradiol patch use, the overall annual pregnancy rate was 0.8% and the method-failure rate was 0.6%, which is comparable to the pregnancy rates observed with use of COCs (10). Fifteen pregnancies were reported in women who used Ortho Evra. Of those, 5 occurred in women weighing > 198 lbs, suggesting that Ortho Evra may be less effective in women with higher body weights. The reason for this is not clear, but it has been suggested that an increase in subcutaneous fat may impair drug absorption. The most common adverse effects of the patch were similar to COCs and included breast symptoms (22%), headache (21%), application site reaction (17%), nausea (17%), upper respiratory tract infection (10%), dysmenorrhea (10%), abdominal pain (9%). Approximately 2% of users experienced skin irritation at the application site.

As with NuvaRing, Ortho Evra provides an alternative delivery method to COCs with a similar safety and efficacy profile. Primary concerns include patch detachment and the unresolved issue of decreased efficacy in larger women.

Conclusion

The indications and contraindications for Ortho Evra and NuvaRing are identical to those for COCs. Offering less frequent dosing, the primary advantage over oral therapy is the possibility of enhanced user compliance. However, in clinical trials, higher compliance rates were coupled with higher treatment withdrawal rates. Efficacy in a clinical setting is similar to COCs; and in theory, these agents should provide similar noncontraceptive benefits. Serious risks, such as thromboembolism, are expected to be the same as those associated with oral contraceptives. Unique disadvantages of the newer agents include problems associated with delivery such as spontaneous detachment of the patch or expulsion of the vaginal ring. Furthermore, it is unknown how safety and efficacy in a nonclinical, "real-world" setting will compare to clinical trial data. While the lowest expected failure rates in clinical trials of COCs are 0.1% per year, failure rates with typical use may actually be up to 5% per year. Given the disparity observed with COCs, it is likely that NuvaRing and OrthoEvra a gap between failure rates with perfect use and typical use will also become apparent.

When compared to generic combined oral contraceptives, Ortho Evra and NuvaRing are costly alternatives. The availability of generic COCs is increasing. New generic versions of Ortho Novum 7/7/7, Ortho Cyclen, Triphasil, and Tri-Levlen have recently been approved and are likely to be cost-effective first-line agents as prices become competitive. NuvaRing and Ortho Evra are priced similar to second-line brand COCs and are therefore recommended for patients who are intolerant of or have poor compliance with generic COCs.

Reviewed by Lisa Sprague, M.D. Women's Health, Northeast Health Center, Multnomah County Health Department and Nanette Bultemeier, Pharm.D., Assistant Professor of Pharmacotherapy, OSU College of Pharmacy

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Cost Comparison

Phasic	Brand Names	Generic Components (various strengths)	Cost for 28 days*	Generic Option?
Mono-	NECON, NORETHIN, NORINYL, NORTREL, ORTHO-NOVUM, MODICON	NORETHINDRONE -ETHINYL ESTRADIOL	$24-34	YES
Mono-	APRI, DESOGEN	DESOGESTREL – ETHINYL ESTRADIOL	$27-31	YES
Mono-	CRYSELLE, LO/OVRAL, LOW-OGESTREL	NORGESTREL-ETHINYL ESTRADIOL	$18-40	YES
Mono-	AVIANE, ALESSE, LESSINA, LEVLEN, LEVLITE, LEVORA, NORDETTE, PORTIA	LEVONORGESTREL-ETHINYL ESTRADIOL	$29-34	YES
Mono-	DEMULEN, ZOVIA	ETHYNODIOL DIACETATE-ETHINYL ESTRADIOL	$30-37	YES
Bi-	KARIVA, MIRCETTE	DESOGESTREL-ETHINYL ESTRADIOL	$28-34	YES
Tri-	ENPRESSE, TRI-LEVLEN, TRIPHASIL, TRIVORA	LEVONORGESTREL-ETHINYL ESTRADIOL	$27-32	YES
Mono-	YASMIN 28	DROSPIRENONE-ETHINYL ESTRADIOL	$31	NO
Tri-	TRI-NORINYL, ORTHO TRI-CYCLEN	NORETHINDRONE-ETHINYL ESTRADIOL	$36-38	NO
Mono-	OVCON	NORETHINDRONE-ETHINYL ESTRADIOL	$37	NO
Mono-	ORTHO-CYCLEN	NORGESTIMATE-ETHINYL ESTRADIOL	$39	YES
Mono-	NUVARING	ETONOGESTREL-ETHINYL ESTRADIOL	$40	NO
Mono-	LOESTRIN	NORETHINDRONE ACETATE-ETHINYL ESTRADIOL	$45	NO
Mono-	ORTHO EVRA	NORGESTREL-ETHINYL ESTRADIOL	$47	NO
Mono-	LUNELLE	ESTRADIOL CYPIONATE - MEDROXYPROGESTERONE ACETATE	$54	NO

*AWP reported by FirstDataBank 11/1/02

Lunelle Recall

In October, Pharmacia announced a voluntary recall of prefilled syringes containing Lunelle Monthly Contraceptive Injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension) due to lack of assurance of full potency and possible risk of contraceptive failure. The affected lots were distributed in the United States, Puerto Rico and the U.S. Virgin Islands during 2002 and all physicians, pharmacies, clinics and wholesalers who received these lots are being notified. Lunelle package in vials is not affected. Providers are asked to: 1) Contact all patients using Lunelle. Recommend additional barrier methods of birth control and perform a pregnancy test (Pharmacia will provide pregnancy kits and condoms free of charge to those who request them) and 2) Discontinue using and dispensing all Lunelle prefilled syringe lots and promptly return any inventory.

For further information healthcare professionals may call the Pharmacia medical information service on (800) 323-4204. Patients may call the Pharmacia patient information service on (888) 691-6813. You may also refer to the FDA website at http://www.fda.gov/oc/po/firmrecalls/pharmacia10_02.html .
Affected product lot numbers are available at http://www.fda.gov/medwatch/SAFETY/2002/lunelle_deardoc.htm .

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