GENERAL GYNECOLOGY

Transdermal hormonal contraception: benefits and risks

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Transdermal drug delivery systems, which provide continuous administration of ≥1 drugs through the skin, maintain constant plasma drug levels and avoid the peaks and troughs of oral administration. The use of a patch avoids the loss of bioavailability from first-pass hepatic metabolism and enzymatic degradation in the gastrointestinal tract that oral drug administration confers, thus permitting lower doses of drug to achieve a therapeutic effect.

Continuous delivery may reduce systemic side-effects, particularly those that are associated with high plasma levels. Multiday dosing, made possible by sustained delivery of drugs with short half-lives that would require frequent dosing if taken orally, improves patient compliance. Other advantages of transdermal patches include their nonoral route in patients who are unable to take oral medications and the immediate cessation of drug administration with removal.

Because patch size limits the amount of drug that can be delivered, the drug molecule must be potent. The first generation of patches, which used a reservoir system, led to a high incidence of local skin reactions and adhesion problems. The newer matrix systems, however, have reduced these problems substantially.

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OVERVIEW
The author evaluates evidence of the safety, efficacy, satisfaction level, and other factors that are related to the use of the transdermal contraceptive patch.

★ EDITORS' CHOICE ★

Transdermal Hormonal Contraception

The Food and Drug Administration approved the first transdermal contraceptive patch, Ortho Evra (Ortho-McNeil Inc, Raritan, NJ), which is a matrix system that contains 6.0 mg norelgestromin (formerly called 17-deacetylnorgestimate) and 0.75 mg ethinyl estradiol (EE), in November 2001. Norelgestromin is the primary active metabolite of norgestimate, which is a progestin that has been used in combination with EE as an oral contraceptive (OC) since 1986. One patch is applied once weekly for 3 consecutive weeks followed by a patch-free week. During the 7-day wear period, the patch delivers continuous levels of hormones, which avoids the peaks and troughs of OCs.

Prescribing Information Update

Ortho-McNeil Pharmaceutical, the manufacturer of the Ortho Evra patch, in conjunction with the Food and Drug Administration has amended the prescribing information based on results from 2 epidemiologic studies. The pharmacokinetic profile for the Ortho Evra patch is different from that for OCs in that it has higher steady-state concentrations and lower peak concentrations. Area under the curve and average concentration at steady state for EE are approximately 60% higher in women who use Ortho Evra vs those who use an OC that contains 35 μg EE. In contrast, peak EE concentrations are approximately 25% lower in women who use Ortho Evra.

Intersubject variability results in increased exposure to EE in some women who use either Ortho Evra or OCs. However, intersubject variability in women who use Ortho Evra is higher. Whether different pharmacokinetic profiles of EE in women who use Ortho Evra vs those who use OCs that contain 35 μg EE alter risk for serious adverse events is unknown. Increased estrogen exposure may increase such risk, including a risk for venous thromboembolism (VTE).

Epidemiologic Studies

A recent nested case-control epidemiologic study evaluated the risk for nonfatal VTE based on data from a US-based company that collects insurance claims information that is paid by managed-care plans. The odds ratio that compared the patch and OCs was 0.9 (95% CI, 0.5-1.6). The overall incidence rate for VTE was 52.8 per 100,000 woman-years (95% CI, 35.8-74.9) among patch users and 41.8 per 100,000 woman-years for users of norgestimate-containing OCs (95% CI, 29.4-57.6).

The investigators of another case-control study examined insurance claims information from a database and medical record verification of study outcomes. The odds ratio for VTE risk in current users of the patch to current users of OCs was 2.42 (95% CI, 1.07-5.46). The estimated incidence of VTE per 100,000 woman-years was 40.8 for contraceptive patch users vs 18.3 for users of the norgestimate-containing OC. VTE is a rare event and has been reported as a potential risk of all hormonal contraceptive therapy. The absolute risk of symptomatic VTE in pregnancy is 50-300 events per 100,000 pregnancies.

Efficacy

Overall and method failure Pearl indices for the transdermal contraceptive patch are comparable with those of 2 OC for-

TABLE
Most common adverse events in the comparative study of the patch vs an OC

	Overall incidence (%)		
Adverse event	**Patch (n = 812)**	**OC (n = 605)**	***P* value**
Headache	21.9	22.1	.95
Nausea	20.4	18.3	.34
Application site reaction	20.2	NA	NA
Breast symptoms*	18.8	6.1	<.001
Upper respiratory tract infection	13.3	17.9	.02
Dysmenorrhea	13.3	9.6	.04
Abdominal pain	8.1	8.4	.85

Adapted from Sibai BM, Odlind V, Meador ML, Shangold GA, Fisher AC, Creasy GW. A comparative and pooled analysis of the safety and tolerability of the contraceptive patch (Ortho Evra/Evra). Fertil Steril 2002;77(suppl 2):S19-26. With permission from the American Society for Reproductive Medicine.

* Include breast discomfort, engorgement, and pain.

mulations. However, a post hoc analysis of pooled data across 3 pivotal phase III clinical trials showed that the transdermal contraceptive patch may be less effective in women with a body weight of ≥198 lb (90 kg) than in women with lower body weights.

Cycle Control

In pooled-cycle control data, the contraceptive patch demonstrated a low incidence of breakthrough bleeding with or without breakthrough spotting. In comparative trials, no statistically significant difference was noted between the contraceptive patch and OC groups in the incidence of breakthrough bleeding during any cycle.

Safety and Tolerability

With the exception of application site reactions, which are unique to patch wear, the patch is well-tolerated and has a profile of adverse events similar to that of OCs (Table). The most frequent adverse events are headache and nausea. Breast symptoms that included discomfort, engorgement, and pain occurred in significantly more patch users than in OC users during cycles 1 and 2 ($P < .001$) and, with continued patch use, decreased to zero during cycle 13. The incidence of dysmenorrhea was significantly greater in patch users than in OC users (13.3% vs 9.6%, respectively; $P = .04$). Application site reactions led to discontinuation of use in 2.6% of the women studied.

Adhesion

In clinical trials, only 1.8% of patches were replaced because they fell off; 2.9% of patches were replaced because of partial detachment. Among participants who were enrolled at centers in warm humid climates, the rates of complete or partial detachment were 1.7% and 2.6%, respectively.

Compliance

Women of all ages in the clinical trials were able to use the patch more consistently and correctly than OCs. In the trial that compared the use of the patch with that of levonorgestrel 50/75/125 μg plus E 30/40/30 μg for up to 13 cycles, the percentage of total cycles with reported perfect use was significantly greater for patch users than for OC users (88.7% vs 79.2%, respectively; $P < .001$). Among women <20 years old, the percentage of cycles with perfect use was 67.7% for OC users vs 87.8% for patch users.

Extended Use

Investigators compared the bleeding profiles and degree of satisfaction in women wearing the patch continuously vs those maintaining the conventional 21 days of active therapy with 1 patch-free week. Healthy, regularly menstruating women (n = 239) were assigned randomly (2:1 ratio) to receive the transdermal patch in an extended regimen (weekly application for 12 consecutive weeks, 1 patch-free week, and 3 more consecutive weekly applications; n = 158) or the cyclic regimen (4 consecutive cycles of 3 weekly applications and 1 patch-free week; n = 81).

Extended vs cyclic use of the transdermal contraceptive patch resulted in fewer median bleeding days (6 vs 14, respectively; $P < .001$), bleeding episodes (1 vs 3, respectively; $P < .001$), and bleeding or spotting episodes (2 vs 3, respectively; $P < .001$) during days 1-84. Median numbers of bleeding or spotting days were similar between regimens (14 vs 16, respectively; $P = .407$) during the same period. Extended use delayed median time to first bleeding to 54 days vs 25 days with cyclic use ($P < .001$).

Patient Satisfaction

Women who used the transdermal contraceptive patch gave higher ratings than OC users to emotional and physical well-being and improvements in premenstrual symptoms. In a large, randomized, open-label comparative trial that was conducted in Europe and South Africa, women who used the transdermal patch for either 6 or 13 cycles rated emotional well-being either somewhat or much better at the last cycle than the women who used an OC that contained 150 μg desogestrel and 20 μg EE (30.7% vs 24.1%; $P < .01$).

Comment

The transdermal contraceptive patch has been used by >5 million women. Recent epidemiologic studies (1 study showed increased risk for VTE with the patch vs OC use, and the other study showed no increased risk) and a subsequent label update have provided additional information regarding the risk for serious adverse events with Ortho Evra vs OCs. Women who have cancer or who are predisposed to blood clots, heart attack, or stroke are not candidates for the contraceptive patch. Possible increased risk for such events should be discussed with patients who consider trying the patch.

For appropriate candidates, the patch remains a safe and effective method of contraception. Clinical trials have shown that a significantly greater percentage of women who used the patch used their method more consistently and correctly than did those women who used OCs. The transdermal contraceptive patch offers an alternative for women who are seeking a hormonal contraceptive that may be easier to use than OCs and perhaps more suitable for today's active lifestyles.

CLINICAL IMPLICATIONS

- The transdermal contraceptive patch is a safe and effective option for many patients with a side-effect profile similar to that of oral contraceptives.
- Conflicting data suggest possible increased risk for thromboembolism from the patch vs oral contraceptives, although less than during pregnancy.
- Most users of transdermal oral contraception are satisfied and able to use the method correctly. ■