Evaluation of Contraceptive Efficacy and Cycle Control of a Transdermal Contraceptive Patch vs an Oral Contraceptive
A Randomized Controlled Trial

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Worldwide more than 100 million women choose hormonal contraception for family planning,1 with more than 12 million users in the United States alone.2,3 Combined oral contraceptives (OCs) are widely used because of the efficacy demonstrated in clinical trials and the established safety from postmarketing surveillance.4 However, while clinical trials have shown that correct and consistent use of OCs results in a first-year failure rate of 0.1%,5 the 1995 National Survey of Family Growth (US data) estimated that actual first-year failure rates during typical use of OCs range from 7.3% to as high as 8.5%.6 Noncompliance is the primary reason cited to explain this difference.7-9 There is clearly a need for reversible contraceptives with a more convenient dosing schedule that would enhance patient compliance and achieve high contraceptive efficacy in typical use.

The transdermal contraceptive patch has been evaluated as a new method of contraception in several trials. Phar-
methods

study design

this study was a randomized, active control, multicenter clinical trial comparing the contraceptive patch with an OC. the study was conducted at 39 centers in the United States and 6 centers in Canada from October 1997 to June 1999. the protocol was approved by the institutional review board or ethics committee at each center, and the study was conducted in compliance with the regulations governing good clinical practice. all sites were visited regularly during the trial by study monitors to ensure adherence to study procedures. after giving informed consent, 1400 participants were to be randomized in a ratio of 4:3 to receive either the contraceptive patch (ORTHO EVRA/EVRA, a 20-cm² patch designed to deliver 150 µg of norelgestromin and 20 µg of ethinyl estradiol daily to the systemic circulation,¹⁰ have been published.¹¹⁻¹⁴ this study is the first published clinical trial of transdermal contraception. the objective of this study was to compare the transdermal contraceptive patch and an OC in terms of contraceptive efficacy, cycle control, compliance, and safety. the a priori hypotheses were that the contraceptive patch would be comparable to the OC with respect to contraceptive efficacy, cycle control, and safety but better than the OC with respect to compliance.

randomization and blinding

an interactive voice-activated randomization system was used to randomize participants to treatment within centers by permuted blocks. randomization was performed by the r.w. johnson pharmaceutical research institute.

study population

a total of 1417 healthy women aged 18 to 45 years were randomized and received the study drug. participants had to be sexually active and at risk of pregnancy; have regular menstrual cycles; have at least 1 normal menses since removal of an intrauterine device or progestin implant (norplant) if applicable; have a negative serum β-human chorionic gonadotropin pregnancy test at screening and a negative urine pregnancy test at admission; have had systolic/diastolic blood pressure less than 140/90 mm Hg; be within 35% of ideal body weight; agree to use only the assigned study drug as contraception and not to use any other steroid hormonal therapy other than topical corticosteroids; and provide written informed consent. exclusion criteria included lactation or pregnancy within 42 days of study admission; any disorders that were contraindications to steroid hormonal therapy; uncontrolled thyroid disorder; Papanicolaou test evidence of squamous intraepithelial lesions or adenocarcinoma or other malignancy; history or presence of dermal hypersensitivity in response to topical application; smoking in women older than 35 years; alcohol or substance abuse within 12 months of screening; receipt of injectable progestin (Depo-Provera) within 6 months of screening; and receipt of any experimental drug, device, or hepatic enzyme-inducing drug within 30 days of screening.

patch description and use

the matrix patch is thin and consists of 3 layers: an outer protective layer of polyester; a medicated, adhesive middle layer; and a clear, polyester release liner that is removed prior to patch application. participants in the patch group were instructed to apply the patch to the buttocks, upper outer arm, lower abdomen, or upper torso (excluding the breast). new patches could be applied to sites near the patch that was removed, but not to the same site as the preceding patch. participants could maintain their usual activities, including bathing and swimming, while wearing the patch, but were instructed not to apply oils, creams, or cosmetics on or around the area of patch placement. participants were instructed to apply the patch on the same day of each week (1 patch per week) for 3 consecutive weeks followed by a patch-free week. patches were to adhere on their own, and no supplemental tape or adhesive was permitted. in the event of detachment, patches could be immediately reapplied. patches that did not fully adhere on their own were to be replaced. the replacement patch would then be worn for the remainder of that week.

study evaluations

sample size determination. the sample size was chosen to provide 400 person-years of observation for the contraceptive patch. this was achieved among participants who were enrolled for either 13 cycles or 6 cycles. current regulatory guidance¹³ specifies that studies should be at least large enough to provide an overall Pearl Index with a 95% confidence interval (CI) so that the difference between the upper limit of the CI and the point estimate does not exceed 1 pregnancy per 100 person-years. for a Pearl Index of 1, this is achieved with 400 person-years.

the primary end point for cycle control was breakthrough bleeding and/or spotting during cycle 3. it was anticipated that 11% of the participants in the contraceptive patch group would have breakthrough bleeding and/or spotting during cycle 3. the study was designed with a 4:3 ratio of participants...
using the patch to the OC, so that a difference between treatment groups of 6% (17% of participants in the OC group) could be detected at the .05 level of significance with power of 0.82, assuming available data for 80% of the participants enrolled.

Contraceptive Efficacy. The primary outcome measure for this trial was contraceptive efficacy. The criteria for evaluating contraceptive efficacy included calculation of the Pearl Index (number of pregnancies per 100 person-years of use) and life-table estimates of the probability of pregnancy. Each participant was to have a urine pregnancy test performed 10 days after the scheduled termination cycle or on early withdrawal. All pregnant participants were to have an ultrasound. Pregnancies were classified into the following 4 categories based on available data from the investigators (ultrasound, diary cards, and narratives): (1) pretherapy, in which the estimated date of conception preceded start of the study drug; (2) posttherapy, in which the estimated date of conception was after the last cycle of therapy; (3) method failure during therapy, in which the estimated date of conception was during the cycles of therapy and there was information that the participant complied with dosing; and (4) user failure during therapy, defined as in number 3 except that available information indicated that the participant failed to comply with dosing on, or immediately contiguous with, the date of conception. Follow-up information regarding the pregnancy outcome and any postnatal sequelae in the infant were obtained in all cases. All participants who did not return for a scheduled visit were to be contacted first by telephone and then by certified letter requesting study data. Only participants who failed to respond to telephone calls and the certified letter were considered lost to follow-up.

Cycle Control. Cycle control was evaluated from information recorded on diary cards, which were completed daily by participants. Breakthrough bleeding and spotting was any bleeding and spotting occurring on days 1 through 21, excluding bleeding contiguous with menses. Breakthrough bleeding was defined as requiring sanitary protection of more than 1 pad or tampon on any of those days. Amenorrhea was defined as 2 continuous cycles without any bleeding or spotting.

Compliance. Compliance was determined by daily dosing (and patch replacement) noted on diary cards and included all cycles in which adequate dosing information was available. Perfect compliance was defined as 21 consecutive days of drug taking, which could have included the use of replacement patches, followed by a 7-day drug-free interval. For patch users, no patch could be worn for more than 7 days.

Patch Adhesion. Patch replacement information was used to assess patch adhesion. The percentage of patches replaced for the reason of “fell off” was summarized as patches that completely detached due to lack of adherence. The percentage of patches replaced because of partial detachment was also summarized.

Safety. Adverse events, both those reported by participants and those observed by study center personnel, were documented throughout the study. Clinical laboratory tests (hematology and serum chemistry), vital signs (blood pressure, pulse rate, and temperature), and physical and gynecologic examinations were performed prestudy and at the final visit.

Statistical Methods
Pregnancy rates were estimated by Pearl Index and life-table analyses and were based on all pregnancies occurring during therapy and the total number of cycles during therapy through cycle 13, with data censored after the cycle of conception. The Pearl Index was calculated as [(number of pregnancies × 1300)/number of cycles during therapy]. Under a modified intent-to-treat analysis, all participants who received the study drug for at least 1 day and were not pregnant at the start of cycle 1 were included in the evaluation of efficacy. The overall Pearl Index includes all pregnancies in the modified intent-to-treat population. The method-failure Pearl Index, which included only those pregnancies in which there was not a concurrent dosing error, was also calculated. Kaplan-Meier estimates of the probability of pregnancy at cycles 6 and 13 were used to summarize the results by treatment group. Estimates were obtained at cycle 6 since all participants were to complete this cycle. Participants who had not become pregnant were censored at their last cycle on treatment. Treatment group comparisons were conducted using the log-rank test. For both Pearl Indexes and life-table estimates of the probability of pregnancy, 95% CIs were calculated for each treatment group. The 95% CI for the Pearl Index was derived using a variance obtained by the delta method.

A key end point for the evaluation of cycle control was the incidence of breakthrough bleeding and/or spotting during cycle 3. Treatment differences were evaluated by a χ² test to compare the percentage of participants with the event. Supportive cycle control data included an evaluation of breakthrough spotting, breakthrough bleeding, and amenorrhea over all cycles.

To compare the 2 treatment groups with regard to the proportion of each participant’s cycles in which there was perfect compliance, a t test was used in which the participant was the experimental unit. Although not directly compared due to the correlation of results across cycles within an individual, compliance rates across cycles were calculated.

For the most frequently reported adverse events, the Fisher exact test was used to compare the proportion of participants with the event and the proportion of participants in which it was a treatment-limiting event.

For vital signs and hematology and chemistry data, the mean changes at the last visit from baseline were analyzed using the t test. All participants who took the study drug were evaluable for safety. Safety was assessed by the following: adverse
events, mean changes from baseline in hematology and serum chemistry parameters and vital signs, and changes in physical and gynecologic examinations.

**RESULTS**

**Demographic Characteristics and Disposition**

The demographics of the 2 treatment groups were comparable (TABLE 1). Approximately 22% of the participants had not used OCs within the past 2 months, and 55% switched directly from OCs to their assigned study treatment (ie, were using OCs in the cycle prior to study start); 8% switched indirectly (ie, within 2 months, but not in the cycle immediately prior to start) from OCs; and for 15%, data were not provided. FIGURE 1 shows the allocation of participants following randomization and includes the number distributed to 6 and 13 cycles of study drug use. There were 812 participants treated with the patch, and 70% completed the study; 605 participants were treated with the OC, and 76% completed the study. One participant in the patch group was excluded from the efficacy analyses because she had a pretreatment pregnancy and began using the study drug in violation of the protocol. All 1417 participants treated were included in the safety analyses.

**Contraceptive Efficacy**

The overall and method-failure Pearl Indexes were numerically lower in the patch group (1.24 and 0.99, respectively) than in the OC group (2.18 and 1.25, respectively), although the differences between the treatments were not statistically significant (P=.57 and P=.80, respectively) (TABLE 2). In the patch group, 4 method-failure pregnancies and 1 user-failure pregnancy occurred among 811 women treated for 5240 cycles. In the OC group, 4 method-failure and 3 user-failure pregnancies occurred among 605 women treated for 4167 cycles.

The life-table analyses indicated that the probability of pregnancy through 6 or 13 cycles was also lower with the patch than with the OC (TABLE 2). TABLE 3 provides a profile of each of the 12 pregnancies that occurred during therapy.

**Cycle Control**

The incidence of breakthrough bleeding is presented for representative cycles in FIGURE 2A. There were no statistically significant differences between the patch and the OC with respect to break-
through bleeding at any cycle. The incidence of breakthrough bleeding and/or spotting is presented for representative cycles in Figure 2B. For cycles 1 and 2, the patch group had significantly higher rates of breakthrough bleeding and/or spotting, but in subsequent cycles the 2 groups did not differ significantly. Amenorrhea occurred in 0.1% of patch users and 0.2% of OC users.

Compliance

Compliance with the dosing schedule of the patch was better than that of the OC. The mean proportion of each participant’s cycles that demonstrated perfect compliance was 88.2% (811 total participants, 5141 total cycles) with the patch and 77.7% (605 total participants, 4134 total cycles) with the OC (P < .001). Overall, the percentage of cycles in which there was perfect compliance was 88.7% (4558/5141) with the patch and 79.2% (3276/4134) with the OC.

Patch Adhesion

A total of 4.6% of all patches were replaced for either complete (1.8% [300/16673]) or partial (2.8% [470/16673]) detachment.

Safety

There were no unexpected adverse events with either treatment. The most frequent adverse events and the percentage of participants who discontinued therapy for each adverse event are listed in Table 4. With the exception of mild-to-moderate application site reactions in the patch group, the types of adverse events were similar in the 2 treatment groups. The frequency of application site reactions did not increase over time. The overall occurrence of breast discomfort was higher for the patch than for the OC. This difference was significant only in cycles 1 and 2 (15.4% vs 3.5% in cycle 1 [P < .001] and 6.6% vs 1.5% in cycle 2 [P < .001]). For cycles 3 to 13, the by-cycle incidence of breast discomfort was not significantly different between treatments (P ≥ .10 for cycles 3-13; 3.2% to 0% vs 1.7% to 0%, respectively). For those participants with breast discomfort, 85% rated the discomfort as mild-to-moderate in severity. Dysmenorrhea was also more frequent in the patch group. The most common adverse events causing treatment discontinuation were application site reactions, nausea, headache, dysmenorrhea, and breast discomfort. Headache and dysmenorrhea, although infrequent causes of discontinuation, were significantly more likely to be treatment limiting in the patch group. For both the patch and OC, approximately 2% of participants (patch 16/812, OC 11/605) reported a serious adverse event, and these events were generally similar between treatments. The serious adverse events that occurred with the patch included injury (3 participants), cholecystitis (1), abdominal pain (3), pyelonephritis (1), nausea/vomiting/pharyngitis (1), pain (1), migraine (1), dehydration (1), sleep disorder (1), diabetes mellitus (1), and manic-depressive psychosis (1). The serious adverse events that occurred with the OC included injury (3 participants), cholecystitis (1), abdominal pain (1), pyelonephritis (2), pharyngitis (1), pelvic inflammatory disease (1), intracranial hypertension (1), and depression/suicide (1). Three serious adverse events were considered possibly or likely related to the use of the patch, including 1 case of pain and paraesthesia in the left arm, 1 case of migraine, and 1 case of cholecystitis. All 3 of these events resolved, although the cholecystitis required cholecystectomy. Two serious adverse events were considered possibly

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<th>Table 2. Contraceptive Efficacy Through 13 Cycles of Treatment*</th>
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<td>Method failure, % (95% CI)</td>
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* CI indicates confidence interval.
† Kaplan-Meier estimates of the cumulative probabilities of pregnancy; 6-cycle participants are included in the 13-cycle results.

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<tr>
<th>Table 3. Summary of All Pregnancies That Occurred During Therapy</th>
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<td>Method (M) Failure vs User (U) Failure Age, y Weight, kg Prior Oral Contraceptive Use Cycle of Conception</td>
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related to the use of the OC, and they included increased intracranial pressure, which did not resolve, and severe depression leading to suicide.

There were no clinically meaningful changes in laboratory parameters, vital signs, or physical or gynecologic examination findings, although total cholesterol concentrations increased from baseline to the end of therapy by a mean of 15.8 mg/dL (0.41 mmol/L) and 8.1 mg/dL (0.21 mmol/L) in the patch and OC groups, respectively (P < .001). Triglyceride levels increased more in the patch group (9.7 mg/dL [0.11 mmol/L]) than in the OC group (0.9 mg/dL [0.01 mmol/L]) (P = .008).

In both treatment groups, mean body weight increased from baseline to the end of therapy by 0.41 kg.

**COMMENT**

Compliance problems with OCs have been well documented. For example, in a compliance study by Rosenberg and colleagues, almost 50% of OC users reported missing 1 or more pills per cycle, with 22% missing 2 or more pills. In another compliance study, an electronic device that monitored the time and date of pill removal from the container indicated that 30% to 51% of women skipped 3 or more dosing days per cycle. While many factors contribute to less than perfect compliance with daily OC dosing, women who do not have a regular pill-taking routine and those who do not read and understand the dosing instructions are at greatest risk for poor compliance. Contraceptive compliance is clearly related to contraceptive efficacy. United States prescribing information for contraceptive products summarizes failure rates for all methods of contraception from National Survey of Family Growth data. Long-acting hormonal contraceptives that require infrequent patient activity toward compliance (eg, progestin implants, 3-month progestin injectables) have reduced contraceptive failures associated with noncompliance. This can be seen by the small difference between the “perfect-use” (method) failure rate and “typical-use” (method failure plus user failure) failure rate.

The contraceptive efficacy of the patch in this randomized clinical trial was compared with that of an OC. The “overall” Pearl Index and probability of pregnancy through 13 cycles were nu-
matically lower for the contraceptive patch compared with the OC, but the sample size was relatively small and this difference was not statistically significant. The numerically lower overall failure rate for the contraceptive patch may be due to the better compliance shown with this once-weekly dosing regimen vs the daily dosing for the OC. A significant difference in compliance with the patch vs an OC has been reported in another randomized clinical trial. Evidence that better compliance may have played a role in the lower overall pregnancy rate for the contraceptive patch can be found by comparing the overall and method failure rates for the patch and the OC, similar to comparing the typical-use (overall) and perfect-use (method) failure rates for long-acting hormonal methods. The method failure rate, which excludes pregnancies associated with noncompliance, is similar for the contraceptive patch and the OC (0.99 vs 1.25). A contraceptive with high compliance would be associated with an overall failure rate (method failure plus user failure) that is very similar to the method failure rate alone, as seen with the contraceptive patch (1.24 vs 0.99). A contraceptive with lower compliance would have a greater difference between the overall failure rate and the method failure rate due to more user failures, as seen with the OC (2.18 vs 1.25). Additional evidence that better compliance contributed to the low probability of pregnancy with the contraceptive patch is seen from analysis of 6-cycle data, a treatment duration that all randomized participants were to complete. After 6 cycles, the overall probability of pregnancy with the new transdermal contraceptive was half that of the OC (0.6% vs 1.2%) while the method failure probability of pregnancy was nearly the same (0.4% vs 0.6%); however, neither of these differences was statistically significant. Given that at least 63% (891/1417) of the participants in this trial (direct plus indirect switchers combined) were experienced OC users, the significantly higher compliance shown for the transdermal contraceptive method (even in experienced OC users) could result in lower typical-use failure rates (as reported by the National Survey of Family Growth6) than seen with the OC comparator.

The incidence of unexpected vaginal bleeding with a hormonal contraceptive is commonly reported as a reason for discontinuation of a particular method. Currently, the only available hormonal methods that require less frequent dosing than OCs contain only progestin, and progestin-only methods are associated with frequent episodes of unexpected bleeding when compared with combination estrogen-progestin methods. In this trial, the contraceptive patch had an incidence of breakthrough bleeding that was comparable to the OC at all cycles. The incidence of breakthrough bleeding and/or spotting was significantly higher among patch users only during the first 2 cycles.

The rate of adhesion of a contraceptive patch will also contribute to contraceptive efficacy, cycle control, and patient satisfaction. A total of 4.6% of all patches in this study were replaced for either complete (1.8% [300/16673]) or partial (2.8% [470/16673]) detachment.

Mild-to-moderate application site reactions occurred in the patch group, and 2.6% of participants withdrew from the study as a result. Several dermal studies have been conducted with the contraceptive patch. In these dermal studies, the patch was not associated with either phototoxicity or photoallergy and demonstrated only mild skin irritation in a minority of participants. No other new or unexpected adverse reactions were observed. The incidence of mild-to-moderate breast discomfort was higher with the patch than the OC, only in the first 2 cycles, but the discontinuation rate for breast discomfort was not significantly different between the patch and the OC. Both the contraceptive patch and the OC led to a mean increase in total cholesterol level. In another study, the patch did not significantly change the low-density lipoprotein/high-density lipoprotein ratio when compared with placebo.

The current study design has potential limitations. A double-dummy design to blind the treatments to the participants and to the investigators was considered but not used, since the use of back-up contraception following placebo dosing errors would compromise the assessment of efficacy in the study. The study was not designed to detect differences in contraceptive efficacy. There was a slight imbalance in the percentage of participants who withdrew or were lost to follow-up (29.7% in the patch group and 24.3% in the OC group).
19. Croner BA, Smith RD, Blair JM, Dwyer J, Brown RT. A prospective study of adolescents who choose among levonorgestrel implant (Norplant), medroxyprogesterone acetate (Depo-Provera), or the combined oral contraceptive pill as contraception. Pediatrics. 1995;95(suppl):60S.

One has only to sit in the woods or fields, or by the shore of the river or lake, and nearly everything of interest will come round to him, the birds, the animals, the insects.
—John Burroughs (1837-1921)