Transdermal contraception: Evaluation of three transdermal norelgestromin/ethinyl estradiol doses in a randomized, multicenter, dose-response study

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OBJECTIVE: The objective of this study was to identify the dose for a contraceptive patch that provides a predetermined level of ovulation suppression and cycle control and that is well tolerated.

STUDY DESIGN: In this randomized study, 610 subjects received 10-, 15-, or 20-cm² patch dose sizes (20-cm², Ortho Evra/Evra) (Janssen Pharmaceutica, NV Belgium) or Ortho-Cyclen/Cilest (Janssen Pharmaceutica, NV Belgium) for up to 4 cycles. As with Ortho-Cyclen, patch regimens included 21 dosing days (3 consecutive 7-day patches) followed by 1 dose-free week.

RESULTS: The patch regimens demonstrated a dose-response for ovulation suppression and cycle control. Presumed ovulation, determined on the basis of serum progesterone concentrations ≥3 ng/mL in cycles 1 and 3, occurred in 6.2% (Ortho Evra) and 7.2% (Ortho-Cyclen) of subjects. At cycle 3, breakthrough bleeding/spotting was reported by 10.5% and 15.0% of subjects, respectively. Compliance with each patch was superior to that with Ortho-Cyclen (all P < .001). All regimens had safety profiles typical of oral contraceptives.

CONCLUSION: The 20-cm² patch (Ortho Evra) provided ovulation suppression, cycle control, and safety similar to that of Ortho-Cyclen, with significantly better compliance. (Am J Obstet Gynecol 2002;186:15-20.)

Key words: Norelgestromin, ethinyl estradiol, norgestimate, Ortho Evra

Transdermal delivery systems have been successfully developed for a variety of drugs, with the first transdermal patches becoming commercially available in the early 1980s. Examples of drugs that are currently available in transdermal delivery systems include clonidine, estradiol, estradiol/norethisterone acetate, fentanyl, nicotine, nitroglycerin, scopolamine, and testosterone. A new contraceptive patch (Ortho Evra/Evra) has been developed that offers potential advantages over oral contraceptives (OCs), including greater convenience (ie, once-weekly dosing rather than daily dosing), better user compliance, dosing that is not affected by gastrointestinal disturbances, and elimination of the daily peaks and troughs in progestin and estrogen serum levels seen with oral dosing. Unlike long-acting contraceptives, the contraceptive patch is user controlled and the method is readily reversible.

This study compared 3 patch sizes, each delivering norelgestromin (NGMN) and ethinyl estradiol (EE) to systemic circulation, and a well-established OC product containing norgestimate (NGM) and EE (Ortho-Cyclen/Cilest). Norelgestromin, previously known as 17-deacetylnorgestimate, is the primary active metabolite of NGM. The primary objective of this randomized study was to identify the dose for a contraceptive patch that provides a predetermined level of ovulation suppression and cycle control and that is well tolerated. Secondary objectives were to evaluate the impact of a 1-day delay in patch application or OC ingestion on suppression of ovulation.

Material and methods

Study design. This open-label, parallel-group, 4-cycle trial was conducted at 32 centers in the United States, Europe, and South Africa. The study protocol was approved by the ethics committee at each center or by one of two central institutional review boards, as appropriate. After giving informed consent, subjects were assigned to 1 of 4 groups by use of a computer-generated randomization schedule: 1 of 3 patch sizes (10-cm² patch, which delivers
NGMN 75 µg and EE 10 µg daily to systemic circulation; 15-cm² patch, which delivers NGMN 112.5 µg and EE 15 µg daily to systemic circulation; and 20-cm² patch [Ortho Evra], which delivers NGMN 150 µg and EE 20 µg daily to systemic circulation) or oral NGM 250 µg and EE 35 µg (Ortho-Cyclen). Randomization was balanced by using permuted blocks of size 4 and was stratified by study center. For cycles 1 to 3, patch treatment was 3 consecutive 7-day patches (21 days) followed by 1 dose-free week, whereas OC treatment was 1 pill daily (21 days) followed by 1 dose-free week. At the start of cycle 4, patch application or pill ingestion was intentionally delayed by 1 day. All subjects used a back-up nonsteroidal method of contraception during treatment.

**Study population.** A total of 610 healthy, ovulatory women aged 18 to 45 years were randomized and received study therapy. Subjects were presumed to be ovulatory at baseline on the basis of a serum progesterone concentration of ≥3 ng/mL on at least 1 day during the 7 days before menses (although a peak progesterone level of >3 ng/mL could be the result of luteinization of the follicle in the absence of ovulation), be within 35% of ideal body weight, have regular menstrual cycles, have a negative serum β-human chorionic gonadotropin pregnancy test, and provide written informed consent. Exclusion criteria included heavy smoking; alcohol or substance abuse within 12 months of screening; current evidence of cervical dysplasia; lactation or pregnancy within 60 days of screening; receipt of Depo-Provera within 6 months of screening; or receipt of steroid hormonal therapy. Norplant, an intrauterine device, or hepatic enzyme-inducing drug within 60 days of screening.

**Description and use of study therapy.** The matrix patches were thin, square patches ~1.2 inches (10-cm² patch), 1.5 inches (15-cm² patch), and 1.8 inches (20-cm² patch) on each side and consisted of 3 layers: an outer protective layer; a medicated, adhesive middle layer; and a clear release liner that is removed before patch application. Subjects in the patch groups were instructed to apply the patch to either the right or left side of the lower abdomen; each patch was to be applied to a different area of the abdomen. Subjects 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. In the event of patch detachment before the scheduled change day, a replacement patch was to be applied immediately and worn for the remainder of that week. Subjects who delayed patch application for 3 or more days, required more than 3 replacement patches during the study, or manifested severe skin irritation at the patch site were to be discontinued from study participation.

In this study, subjects who missed 3 consecutive pills in any given cycle were to be withdrawn. Consistent with the United States physician package insert for Ortho-Cyclen, subjects who missed 1 pill were instructed to take the pill at the time the error was discovered. If a subject missed 2 pills, she was instructed to take 2 pills on the day she remembered and 2 pills the next day.

**Study evaluations**

**Ovulation suppression.** Ovulation suppression was determined by measurement of serum progesterone concentrations on days 7, 14, 21, and 28 of cycles 1, 3, and 4. Progesterone levels were determined by SmithKline Beecham Clinical Laboratories (Van Nuys, Calif), a licensed clinical laboratory. A progesterone concentration of ≥3 ng/mL was considered to be evidence of possible ovulation. Luteal activity was defined as the measured serum progesterone concentration within a cycle of ≥1 but <3 ng/mL, and anovulation was defined as the measured serum progesterone concentration within a cycle remaining below 1 ng/mL.

**Cycle control.** Cycle control was evaluated from information recorded on diary cards, which were completed daily by subjects and collected at the monthly visits. Breakthrough bleeding and spotting was any bleeding and spotting occurring on days 1 through 21, excluding early withdrawal flow. Breakthrough bleeding was defined as requiring sanitary protection of more than 1 pad or tampon on any day during the intermenstrual period.

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**Table I. Demographic characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>10-cm² patch (n = 153)</th>
<th>15-cm² patch (n = 157)</th>
<th>20-cm² patch (n = 150)</th>
<th>OC (n = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) Mean (SD)</td>
<td>32.9 (6.57)</td>
<td>32.5 (6.33)</td>
<td>32.0 (6.48)</td>
<td>32.1 (6.42)</td>
</tr>
<tr>
<td>Race (%) W/B/A/O</td>
<td>77/11/1/11</td>
<td>82/7/1/10</td>
<td>80/7/1/11</td>
<td>81/6/2/11</td>
</tr>
<tr>
<td>Height (cm) Mean (SD)</td>
<td>165.2 (6.96)</td>
<td>165.4 (7.22)</td>
<td>165.0 (6.18)</td>
<td>165.4 (6.87)</td>
</tr>
<tr>
<td>Weight (kg) Mean (SD)</td>
<td>66.9 (11.02)</td>
<td>65.9 (11.38)</td>
<td>65.2 (10.91)</td>
<td>65.7 (10.89)</td>
</tr>
<tr>
<td>Previous OC use (%)</td>
<td>Fresh start*</td>
<td>48</td>
<td>40</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Indirect switch†</td>
<td>49</td>
<td>56</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

*OC, Oral contraceptive; W/B/A/O, White/Black/Asian/Other.
†Used OCs within 2 months of study drug start.
Breakthrough spotting was defined as requiring sanitary protection of ≤1 pad or tampon on any day during the intermenstrual period. Amenorrhea was defined as 2 continuous cycles without any bleeding or spotting.

**Pituitary-ovarian activity.** Endogenous pituitary-ovarian activity was assessed in a subset of subjects (~25 per group) by ultrasonographic measurements of ovarian follicle size and by measurement of serum luteinizing hormone (LH) and estradiol concentrations on days 2 (day 3 for cycle 4), 7, 14, 21, and 28 of cycles 1, 3, and 4. For measurements of ovarian follicle size, the maximum mean follicular diameter was defined as the largest of all mean follicular diameters in a given cycle or cycles. Serum LH concentrations of >15 IU/L and estradiol concentrations of >100 pg/mL were considered levels that might be associated with ovulation.

**Compliance.** Compliance was determined by daily dosing (and patch replacement) noted on diary cards. For cycles 1, 2, and 4, perfect compliance was defined as 21 consecutive days of drug taking, followed by a 7-day drug-free interval with no patch worn for more than 7 days. For cycle 3, perfect compliance was defined as 21 consecutive days of drug taking, followed by an 8-day drug-free interval.

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

**Safety.** Data on adverse events, both those reported by subjects and those observed by study center personnel, were collected throughout the study. In addition, application site reactions were recorded by subjects on diary cards. Clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs (blood pressure, pulse rate, and temperature), and physical and gynecologic examinations were performed before the study and at the final visit.

**Statistical methods.** The incidence of presumed ovulation, luteal activity, and anovulation at cycles 1 and 3 combined and at cycle 4 was summarized for all subjects with at least 3 progesterone measurements at the evaluable cycle. Between-regimen differences in ovulation rates were assessed by a χ² test. The protocol-specified criterion for ovulation suppression was the presumed ovulation rate be significantly lower than a rate of 15% at cycles 1 and 3 and 4. The threshold of 15% was based on previous OC clinical trial experience (data on file, RWJPR). To assess the impact of a 1-day delay in patch application or pill ingestion, 2-sided 95% CIs were calculated for within-regimen differences in ovulation rates during cycles 3 and 4.

A key endpoint for the evaluation of cycle control was the incidence of breakthrough bleeding/spotting at cycle 3. The protocol-specified criterion for cycle control was that the breakthrough bleeding/spotting rate be significantly lower than a rate of 20% at cycle 3. The threshold of 20% was based on previous OC clinical trial experience (data on file, RWJPR). Supportive cycle control data included an evaluation by cycle of breakthrough bleeding/spotting and breakthrough bleeding, and amenorrhea over all cycles. Treatment differences with respect to breakthrough bleeding/spotting and breakthrough bleeding were evaluated by a χ² test.

Assessments of pituitary-ovarian function (ie, maximum mean follicular diameter and serum LH and estradiol concentrations) were not subjected to statistical analysis.

At each cycle, a χ² test was used to compare the percentage of subjects who were perfectly compliant (as defined previously) between each of the patch groups and the OC group.

All subjects who took study drugs were evaluable for safety. Safety was assessed by adverse events, mean changes from baseline in clinical laboratory parameters and vital signs, and changes in physical and gynecologic examination findings.

**Results**

**Demographic characteristics and disposition.** The demographics of the 4 treatment groups were comparable (Table I). Approximately 50% of the subjects had used OCs within 2 months of the start of study drug administration, but not in the cycle immediately before start of the study drug. Of the 610 subjects randomized and treated, 568 (93%) completed the study. The proportion of subjects who completed the study did not differ significantly across the 4 treatment groups (Table II).

**Ovulation suppression.** A serum progesterone concentration of ≥3 ng/mL was considered to be evidence of possible ovulation. The 20-cm² patch and the OC provided the greatest degree of ovulation suppression during cycles 1 and 3 combined (Table III and Fig 1). There were no statistically significant differences between the 15- or 20-cm² patch groups and the OC group. Ovulation suppression was less in the 10-cm² patch group than in the other patch groups or the OC group, and this difference was statistically significant. Only the 20-cm² patch and the OC fulfilled the protocol-specified criterion for
Fig 2. A, Incidence of breakthrough bleeding by cycle. *Statistically significantly different versus OC. B, Incidence of breakthrough bleeding/spotting by cycle. *Statistically significantly different versus OC.

Table II. Reasons for early withdrawal

<table>
<thead>
<tr>
<th>Reason</th>
<th>10-cm² patch (n = 153)</th>
<th>15-cm² patch (n = 157)</th>
<th>20-cm² patch (n = 150)</th>
<th>OC (n = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>1 (0.7)</td>
<td>6 (3.8)</td>
<td>6 (4.0)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Subject choice</td>
<td>6 (3.9)</td>
<td>2 (1.3)</td>
<td>3 (2.0)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Noncompliance</td>
<td>4 (2.6)</td>
<td>1 (0.6)</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.7)</td>
<td>3 (1.9)</td>
<td>3 (2.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data presented as n (%). OC, Oral contraceptive.

Table III. Ovulation suppression, luteal activity, and anovulation at cycles 1 and 3

<table>
<thead>
<tr>
<th></th>
<th>10-cm² patch (n = 133)</th>
<th>15-cm² patch (n = 139)</th>
<th>20-cm² patch (n = 129)</th>
<th>OC (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation*</td>
<td>57 (42.9)</td>
<td>16 (11.5)</td>
<td>8 (6.2)</td>
<td>10 (7.2)</td>
</tr>
<tr>
<td>Luteal activity†</td>
<td>13 (9.8)</td>
<td>15 (9.4)</td>
<td>7 (5.4)</td>
<td>6 (4.3)</td>
</tr>
<tr>
<td>Anovulation‡</td>
<td>63 (47.4)</td>
<td>110 (79.1)</td>
<td>114 (88.4)</td>
<td>122 (88.4)</td>
</tr>
</tbody>
</table>

Data are n (%). OC, Oral contraceptive.
*Any progesterone concentrations ≥3 ng/mL.
†Highest progesterone concentration ≥1 ng/mL and <3 ng/mL.
‡Highest progesterone concentration <1 ng/mL.

Table IV. Serum luteinizing hormone and estradiol concentrations at cycles 1, 3, and 4

<table>
<thead>
<tr>
<th></th>
<th>10-cm² patch</th>
<th>15-cm² patch</th>
<th>20-cm² patch</th>
<th>OC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of serum LH concentrations &gt;13 IU/L*</td>
<td>4/29 (13.8)</td>
<td>4/28 (14.3)</td>
<td>2/26 (7.7)</td>
<td>1/26 (3.8)</td>
</tr>
<tr>
<td>Cycle 1, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 2, n/N (%)</td>
<td>11/28 (39.3)</td>
<td>9/29 (31.0)</td>
<td>2/27 (7.4)</td>
<td>1/29 (3.4)</td>
</tr>
<tr>
<td>Cycle 3, n/N (%)</td>
<td>15/28 (53.6)</td>
<td>10/29 (34.5)</td>
<td>3/29 (10.3)</td>
<td>3/28 (10.7)</td>
</tr>
<tr>
<td>Incidence of serum estradiol concentrations &gt;100 pg/mL*</td>
<td>13/29 (44.8)</td>
<td>7/28 (25.0)</td>
<td>2/26 (7.7)</td>
<td>2/26 (7.7)</td>
</tr>
<tr>
<td>Cycle 1, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 2, n/N (%)</td>
<td>20/28 (71.4)</td>
<td>11/29 (37.9)</td>
<td>4/27 (14.8)</td>
<td>6/29 (20.7)</td>
</tr>
<tr>
<td>Cycle 3, n/N (%)</td>
<td>20/28 (71.4)</td>
<td>16/29 (55.2)</td>
<td>4/29 (13.8)</td>
<td>8/28 (28.6)</td>
</tr>
</tbody>
</table>

LH, Luteinizing hormone; OC, oral contraceptive.
*All subjects with data available are included.
ovulation suppression; these regimens had presumed ovulation rates (cycles 1 and 3 combined) that were significantly lower than the predetermined limit of 15%. Within-regimen evaluations showed no statistically significant differences in ovulation suppression between cycles 3 and 4 for any group. Thus, delaying the initiation of cycle 4 by 1 day did not appear to have a significant effect on ovulation rates.

**Cycle control.** Breakthrough bleeding was reported at cycle 3 by 13.0%, 4.2%, 3.6%, and 6.6% of subjects in the 10-, 15-, and 20-cm² patch groups and OC group, respectively (Fig 2, A). Subjects wearing the 20-cm² patch had lower breakthrough bleeding rates compared with subjects wearing the 10-cm² patch (all cycles) or those receiving the OC in cycles 3 and 4, and these differences were statistically significant. The 10-cm² patch was associated with statistically significant higher breakthrough bleeding rates than the 15-cm² patch in cycles 2 and 4 and OC in cycle 2, and the 15-cm² patch had statistically significant lower breakthrough bleeding rates than the OC in cycle 2.

Breakthrough bleeding/spotting was reported at cycle 3 by 17.3%, 11.7%, 10.5%, and 15.0% of subjects in the 10-, 15-, and 20-cm² patch groups and OC group, respectively (Fig 2, B). No statistically significant differences were observed among the 4 treatment groups at cycles 1 or 3. At cycles 2 and 4, the 10-cm² patch had statistically significant higher breakthrough bleeding/spotting rates than each of the other treatment groups. No other statistically significant differences were noted with respect to breakthrough bleeding/spotting rates. The 15- and 20-cm² patches fulfilled the protocol-specified criterion for cycle control.

Amenorrhea occurred in one subject in the 10-cm² patch group only.

**Pituitary-ovarian activity.** Maximum mean follicular diameters (SD) at cycles 1 and 3 combined were 23.6 (9.28) mm, 23.2 (14.79) mm, 12.4 (5.40) mm, and 15.1 (8.15) mm in the 10-, 15-, and 20-cm² patch groups and OC group, respectively. Corresponding mean (SD) serum LH concentrations were 15.1 (15.34) IU/L, 11.4 (4.98) IU/L, 7.0 (3.85) IU/L, and 7.1 (3.65) IU/L; and corresponding mean (SD) serum estradiol concentrations were 186.0 (147.80) pg/mL, 144.2 (142.79) pg/mL, 54.0 (51.29) pg/mL, and 76.2 (78.40) pg/mL. The 20-cm² patch and OC were associated with the lowest incidences of serum LH of >13 IU/L and estradiol of >100 pg/mL (Table IV), concentrations that may be associated with ovulation. For all groups, mean serum LH and estradiol concentrations were generally similar between cycles 3 and 4, although a slightly greater percentage of subjects in each treatment group had higher serum LH concentrations in cycle 4 than in cycle 3 (Table IV).

**Compliance.** At each cycle, the percentage of subjects who were perfectly compliant was significantly higher for each of the patch regimens than the OC (P < .001 for all comparisons) (Fig 3).

**Patch adhesion.** From 0.5% and 0.6% of patches in each of the patch groups were replaced because of complete detachment; approximately half of these detachments occurred in cycle 1.

**Safety.** With the exception of mild-to-moderate and transient application site reactions reported by 3.3%, 5.1%, and 6.7% of subjects in the 10-, 15-, and 20-cm² patch groups, respectively, the adverse events profile was similar in each of the patch groups compared with the OC group. Adverse events that occurred in 10% or more of subjects in any group included headache, upper respiratory tract infection, nausea, dysmenorrhea, influenza-like symptoms, breast pain, sinusitis, back pain, abdominal pain, dyspepsia, pharyngitis, and vomiting. The most common adverse events causing discontinuation were application site reactions (0, 10-cm² patch; 3.2%, 15-cm² patch; 0, 20-cm² patch; 0, OC), nausea (0, 10-cm² patch; 0.6%, 15-cm² patch; 1.3%, 20-cm² patch; 0.7%, OC), headache (0.7%, 10-cm² patch; 0, 15-cm² patch; 1.3%, 20-cm² patch; 0, OC), and vomiting (0, 10-cm² patch; 0.6%, 15-cm² patch; 1.3%, 20-cm² patch; 0, OC). One subject in the 10-cm² patch group experienced a serious adverse event; she was noted to have a nodule on her right breast during cycle 4. A follow-up mammogram was performed ~2 months after the subject completed the study. No malignancy or other pathology was reported.

There were no clinically meaningful changes in laboratory parameters, vital signs, or physical or gynecologic examination findings. None of the subjects became pregnant during the study.

**Comment**

The transdermal contraceptive patch is a unique new method of combination hormonal contraception. The results of this study demonstrate that contraceptive doses of estrogen and progestin can be delivered across the skin
barrier. Although subjects wore all patches on the lower abdomen in this trial, pharmacokinetic data in another study demonstrated that 4 anatomical sites are therapeutically equivalent (outer upper arm, buttocks, torso [excluding breasts], and abdomen). Of the 3 sizes tested, the 20-cm² patch (Ortho Evra), which delivers NGMN 150 µg and EE 20 µg daily to systemic circulation, achieved the protocol-specified criteria for ovulation suppression and cycle control. The 20-cm² patch was comparable to the OC (NGM 250 µg + EE 35 µg, Ortho-Cyclen) for all pharmacodynamic parameters studied. The dosing schedule yielded encouraging results in this study: Delaying the start of cycle 4 by 1 day had no statistically significant effects on ovulation with any of the patches or the OC.

Compliance with the patch regimen was excellent and statistically superior to that observed with the oral tablet. Consistently better compliance was also seen in separate comparative studies of Ortho Evra versus the OCs Merclon and Triphasil. The higher rates of compliance with the patch versus OCs may be related, at least in part, to its once-weekly dosing schedule. Because the patch is replaced weekly on the same day of the week for 3 consecutive weeks (followed by 1 week patch-free) and the next patch cycle begins on the same day of the week, the user need only actively comply with dosing on the same day each week. The superior rate of compliance seen with the patch may help to reduce typical-use failure rates (ie, unintended pregnancies) seen in the United States with use of OCs that have been estimated to be as high as 8%, although this will need to be confirmed in other studies. Patch adhesion was also excellent and improved over time in this study; this trend probably reflects subject learning of the proper application technique with continued use.

In conclusion, the results of this study in healthy ovulatory women demonstrated that the 20-cm² patch (Ortho Evra) provided ovulation suppression, cycle control, and safety similar to that provided by Ortho-Cyclen. Compliance with the dosing schedule of the patch regimens was significantly better than that of Ortho-Cyclen. All 4 regimens were well tolerated and, with the exception of mild-to-moderate application site reactions in the patch groups, each exhibited a safety profile typical of an OC agent. Thus, Ortho Evra represents a new and innovative method of contraception that may meet the needs of many patients and health care professionals.


REFERENCES