

# Transdermal delivery of combined hormonal contraception: a review of the current literature

Rosanna M Galzote<sup>1</sup>

Sally Rafie<sup>2</sup>

Rachel Teal<sup>1</sup>

Sheila K Mody<sup>1</sup>

<sup>1</sup>Section of Family Planning, Department of Reproductive Medicine, University of California, San Diego, <sup>2</sup>Department of Pharmacy, UC San Diego Health, San Diego, CA, USA

**Abstract:** The transdermal patch provides an effective and convenient option for hormonal contraception. The patch currently on the US market contains 150 µg norelgestromin and 35 µg ethinylestradiol (EE). The 20 cm<sup>2</sup> patch is applied once weekly for 3 weeks, followed by a patch-free week, for a 21–7 cycle. Typical failure rates are similar to that of combined oral contraceptives (COCs). Transdermal delivery results in less peaks and troughs of estrogen, but a higher total estrogen exposure compared with COCs. Though studies show mixed results, the risk of developing venous thromboembolism (VTE) is about twice as high with the patch as with COCs; however, the absolute risk of VTE remains low. The side effect profile is similar to that of COCs, with slightly higher rates of breast tenderness plus a unique adverse effect of application site reactions. Two new patches have been developed, one containing gestodene and EE in Europe and another containing levonorgestrel and EE. Overall, the patch provides an alternative to COCs for women who want autonomy and the benefit of not needing to take a pill daily, with similar efficacy and tolerability.

**Keywords:** contraceptive patch, Ortho-Evra, transdermal, levonorgestrel patch, gestodene patch, hormonal patch

## Background

Since the development of the oral contraceptive (OC) pill in the 1960s, hormonal contraception has taken many forms. Combined hormonal contraception (CHC), referring to methods with both estrogen and progestin, can be delivered orally, transdermally, or transvaginally. Although long-acting reversible contraception (LARC) has become more popular, there is still a desire from patients to have a contraceptive method they can control. Additionally, hormonal contraception offers benefits not seen with some of the LARC methods, including improved cycle control and acne treatment. The transdermal and transvaginal contraceptive options give patient autonomy and the benefit of not needing to use the method daily.

The first transdermal delivery system developed in the 1980s was a scopolamine patch. Since then, medications that have been developed in a transdermal form include nicotine, estradiol for hormone therapy, fentanyl, clonidine, nitroglycerin, among others. For successful delivery of a medication through a transdermal system, the molecule must be small and lipophilic to permeate through the skin. Estradiol and ethinylestradiol (EE) are ideal molecules as therapeutic levels can be delivered easily, whereas progesterone and progestins require higher therapeutic levels.<sup>1</sup> The first transdermal contraceptive patch on the US market, Ortho Evra™ (Ortho-McNeil-Janssen Pharmaceuticals Inc., Titusville, NJ, USA), was approved by the US Food and Drug Administration in November 2001.

A transdermal patch offers a number of benefits compared with OCs. There is less variability in plasma concentrations of estrogen, which may decrease estrogen-related

Correspondence: Sheila K Mody  
Section of Family Planning, Department of Reproductive Medicine, University of California, San Diego, 9300 Campus Point Drive, MC 7433, La Jolla, CA 92037, USA  
Tel +1 858 249 1205  
Fax +1 858 657 7212  
Email smody@ucsd.edu

side effects that result from high peak estrogen levels, such as nausea. Though peaks and troughs are minimized, overall estrogen exposure as measured by the area under the concentration curve (AUC) is higher with the Ortho Evra patch compared with the combined oral contraceptives (COCs). A second major advantage is that the user only changes the patch once weekly, as opposed to taking a contraceptive pill daily, which could result in improved adherence. A pooled study of 1,785 patch users showed perfect use ranging from 88.1% to 91.0% across different age groups. In this study, age did not affect adherence. Another study has reported larger differences across age groups.<sup>2</sup> In contrast, perfect use of COCs ranged from 67.7% to 85.2% and differed significantly by age, with lowest rates in <20-year-old females.<sup>3</sup>

## Pharmacology and pharmacodynamics

The Ortho Evra contraceptive patch is a 20 cm<sup>2</sup> adhesive that releases 35 µg EE and 150 µg norelgestromin (NGMN) per day.<sup>4</sup> NGMN is an active metabolite of norgestimate, the progestin contained in the OCs Ortho-Cyclen<sup>®</sup> and Ortho Tri-Cyclen<sup>®</sup>.<sup>4</sup> During development of this product, three patch sizes, 10, 15, and 20 cm<sup>2</sup>, were compared in a study of 610 subjects. It was found that the 20 cm<sup>2</sup> patch achieved ovulation suppression and cycle control similar to that of Ortho-Cyclen (6.2% 20 cm<sup>2</sup> patch, 7.2% Ortho-Cyclen); thus, the only size patch available is the 20 cm<sup>2</sup>.<sup>5</sup>

Reference ranges were set at 0.6–1.2 ng/mL for NGMN and 25–75 pg/mL for EE, as a developmental tool to assess efficacy. The concentrations at steady state are 0.83 ng/mL ±0.21 for NGMN and 56.7 pg/mL for EE, both of which are within the set reference ranges.<sup>4</sup> Compared to the peaks and troughs seen in serum concentrations with the pill, the patch maintains a steadier concentration throughout the day. Serum levels of each stayed within the reference range for the entirety of the 7-day period in the patch's first cycle. Serum levels of NGMN and EE were 20% less if worn on the abdomen compared with the buttock, thigh, or upper arm, though at all sites, the concentration remained within the reference ranges. The mean serum levels of NGMN and EE also remained within the reference range in conditions of heat, humidity, exercise, and cool-water immersion.<sup>4</sup>

One study done in the Netherlands compared mean serum EE concentrations in subjects using the patch (20 µg EE/day), COC (30 µg EE/day), and NuvaRing<sup>®</sup> (Merck & Co., Kenilworth, NJ, USA; 15 µg EE/day). Concentration over time was more variable in COCs compared with the patch and NuvaRing, as the pill had higher peak concentration ( $C_{max}$ )

of 4.5 times than that of the patch and 1.6 times than that of the NuvaRing. The overall exposure to EE, measured by the mean  $AUC_{0-21}$ , was highest for the patch that was 3.4 times that of NuvaRing and 1.6 times that of COCs.<sup>6</sup>

The mechanism of action of NGMN and EE involves 1) thickening the cervical mucus to prevent sperm penetration, 2) decreasing the endometrial receptivity to reduce likelihood of implantation, and 3) inhibiting ovulation by suppressing gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH).<sup>7</sup> Steady state concentration is reached within 2 weeks of patch use, though pregnancy prevention is achieved after 1 week. The half-lives of NGMN and EE are 28.4 and 15.2 hours, respectively. Mean FSH, LH, and estradiol values return to baseline levels 6 weeks after discontinuation.<sup>7</sup>

## Efficacy

An initial open-label 73-center study in 2001 reported an overall failure rate of 0.7% and a method-failure rate of 0.4% through 13 cycles for transdermal delivery. The Pearl index (PI), or number of pregnancies per 100 woman-years, was 0.71 for overall failure and 0.59 for method failure.<sup>8</sup> Similar numbers were reflected in one subsequent study of pooled data from three studies in 3,319 women. Failure rates were 0.8% overall and 0.6% from method failure, corresponding to PIs of 0.88 and 0.7, respectively.<sup>9</sup>

In a large epidemiological trial in the UK, patients prescribed Evra<sup>™</sup> had an incidence of 0.34 unintended pregnancies per 100 women-years. This was higher than the rate with second-generation COCs of 0.16 and 0.12 for third-generation COCs, but lower than progestin-only pills at 0.43. This case-control study was limited as it analyzed prescriptions of contraception, though did not assess actual use of each method.<sup>10</sup> Pooled data of 812 Ortho Evra patch users in the US in a 2004 study showed the impact of compliance on contraceptive efficacy. With perfect compliance, the PI was 0.73. Imperfect dosing increased failure rates to a PI of 2.33 in patch users. They also found that overall, there was a significantly higher proportion of cycles with perfect dosing in patch use compared to OC use (88.7% vs 79.2%).<sup>11</sup>

## Body weight

There was concern over decreased efficacy of transdermal patches in women with higher body weights. Pooled data from three multicenter studies showed significantly increased rates of unintended pregnancy in women ≥90 kg. In women <90 kg, there was no significant association between body weight and pregnancy. Hormone levels decreased with higher body

weight, but analyses showed that only 10%–20% of variability was attributed to body weight.<sup>9</sup>

A prospective study of contraceptive failures in 1,523 CHC users with a high sample size of obese and overweight females did not show body mass index (BMI) to be a significant risk factor for unintended pregnancy. Three-year failure rates did not differ across different BMI categories among CHC users (BMI <25: 8.44%, BMI 25–30: 11.05%, and BMI >30: 8.92%). Failure rates were similar across the three methods: COC, 5.6%; patch, 4.6%; and vaginal ring, 3.4% ( $P=0.22$ ). It is postulated that reduced fertility with increased BMI explains the similar rates of contraception failure.<sup>12</sup>

## Safety

As with any contraceptive containing estrogen, there is a slightly increased risk of developing venous thromboembolism (VTE) with the patch relative to women not on hormonal contraceptives. Given the overall higher exposure to estrogen with the patch (60% greater AUC) compared to COCs, there was concern that this could translate to an increased risk of thromboembolism events compared to women using pills.<sup>13</sup>

In a postmarketing case–control study published in 2006 by Jick et al,<sup>13</sup> nonfatal VTE risk was compared in Ortho Evra patch users and users of the norgestimate-35 (NGM-35) OC, containing norgestimate and 35 µg EE, between 2002 and 2004. They found an overall incidence rate for VTE of 52.8 per 100,000 women-years in patch users and 41.8 per 100,000 women-years in NGM-35 OC users. The odds ratio (OR) for VTE was 0.9 for contraceptive patch users compared to NGM-35 users.<sup>13</sup> A follow-up postmarketing study that included cases up to 2007 found a higher OR of 2.0 (95% CI 0.9–4.1) between patch and COC users, but concluded that the patch does not confer statistically significant excess risk of VTE compared to NGM-35 COC users.<sup>14</sup>

Findings of a study by Cole et al<sup>15</sup> drew different conclusions. The case–control study using private insurance claims data found a significantly increased risk of VTE, myocardial infarction, or ischemic stroke in patch users compared to users of norgestimate-containing COC with 35 µg EE from 2002 to 2004. There was an incidence ratio of 2.2 (95% CI 1.3–1.8) for VTE, with incidences of 40.8 cases per 100,000 woman-years in patch users, compared to 18.3 per 100,000 in norgestimate-containing COC users.<sup>15</sup> A study update by Dore et al<sup>16</sup> had consistent findings. They again found an OR of 2.0 for VTE compared with users of NGM-35 that was significant.<sup>16</sup> The ORs were 0.6 (95% CI 0.1–3.2) for stroke and 1.2 (95% CI 0.3–4.7) for acute myocardial infarction

(AMI). The incidence of stroke and AMI was low, making it difficult to understand the precise risk.<sup>16</sup> Due to these concerns over increased risk of thrombotic events, a black box warning was released by the US Food and Drug Administration (FDA) in 2004 for Ortho Evra labeling and updated again most recently in 2011.

## Utilization

In 2013, 1.6% of women aged 15–44 years in the US used the ring or patch, and 2.6% of women using contraception used either the ring or patch.<sup>17</sup> In a study of focus groups of young women, negative attitudes toward the patch include distrust of effectiveness, as they are not familiar with this method of drug delivery, whereas a pill is more widely accepted as a reliable route. They feared the patch may fall off and held concerns about visibility. There was also concern regarding safety and the increased risk of blood clots in this population. However, many of the women did agree that the patch was easier to remember to use compared to pills.<sup>18</sup>

## Tolerability

Adverse effects of the patch are similar to those of COCs. The most commonly reported complaints and reasons for discontinuation are mild-to-moderate in severity and include application site reactions, nausea, emotional lability, headache, and breast discomfort.<sup>8,19</sup> Weight gain is minimal in patch users, similar to COC users—87.8% of patch users stayed within 5% of baseline body weight.<sup>19</sup> Rates of unscheduled, or breakthrough bleeding (BTB) and spotting were low (<10% BTB, <20% BTB/spotting) and decreased with continued use.<sup>9</sup> Application site reaction is one adverse event unique to the patch. In a pooled study of 812 patch users, there was a 17.4% overall incidence of application site reaction, causing discontinuation in 1.9%. Most reactions (91.4%) were mild-to-moderate in severity.<sup>19</sup> Breast symptoms include breast discomfort, engorgement, and pain. About one-fifth of patch users experienced breast symptoms, mostly in the first two cycles. They were mild-to-moderate in severity in most and decreased over time. Breast symptoms were treatment limiting in 1.9% of participants in a pooled study. In a comparative study, breast symptoms were three times more prevalent in patch users than COC users (18.8% vs 1.6%), but declined to similar rates after the second cycle.<sup>19</sup> Another concern patients express unique to the patch is detachment. The detachment rate is 4.7% with 1.8% being fully detached and 2.9% partially detached. A study shows that adhesion does not differ in conditions of increased heat and humidity or with exercise. Patients are advised to replace patches if they become fully or partially detached.<sup>20</sup>

## Patient satisfaction

In a study of continuation and satisfaction at 12 months of women aged 14–45 years in the Contraceptive CHOICE Project, continuation rates were lowest for the patch at 49.1% compared to other contraceptive methods (55.1% for COCs to 87.5% for LNG-IUD). Only 35.1% of women using the patch reported being very satisfied with the method and 55.7% were not satisfied.<sup>21</sup> The most common reasons for discontinuation of the patch in women in the CHOICE study were not liking “side effects” and logistical reasons. Approximately 41% of patch discontinuers reported side effects.<sup>21</sup>

In contrast, in a small study of 28 adolescents who started Ortho Evra in 2002–2003, 68% were very satisfied and 29% were somewhat satisfied, with 93% stating they would recommend the method to a friend/relative. Despite high satisfaction rates, adolescents discontinue the patch at higher rates than COCs.<sup>22</sup> A prospective longitudinal study comparing adolescent use of contraceptive patch versus pills in 2011 showed after nine cycles that 38% of patch users compared to 60% of pill users had continued the method initiated at enrollment. This is despite both methods having similar satisfaction and patch users reporting that their method improved normal daily activities.<sup>23</sup>

The 1-year contraceptive continuation has been shown to be low among adolescents. In a 12-month longitudinal cohort study of 1,387 women aged 15–24 years, the patch had the lowest continuation rate at follow-up of only 10.9% compared to 32.7% in pill initiators. Additionally, the pregnancy rate in this study was second highest for patch with a PI (pregnancies per 100 person-years) of 30.1.<sup>24</sup> This low rate of continuation in young women was consistent with another study in 2015 of 130 adolescents aged 13–20 years. When offered intrauterine devices (IUDs), injectable, COC, patch, and the ring, 13% opted for the patch. Six-month continuation rates were lowest with the patch and ring at 17%, compared to 88% with the IUD, 20% with the injectable, and 43% with COCs. Of the 23 who chose the patch or ring, 11 never initiated, 2 continued, and 10 discontinued.<sup>25</sup> It is important to note that this was a small study and reasons for not initiating or discontinuing methods were not reported.

## Current patch

Many of the aforementioned studies are on the Ortho Evra patch which has been on the market in the US, but the Evra patch, used in European countries and Canada, has also been studied extensively.<sup>26</sup> This 20 cm<sup>2</sup> adhesive contains 600 µg EE and 6 mg NGMN, releasing 33.9 µg EE and 203 µg NGMN per day. Studies show that Evra users have higher satisfaction and compliance rates than COC users.<sup>27,28</sup> Although the relative

risk for any VTE has shown to be 2.0 compared to corresponding COCs,<sup>29</sup> the Evra patch did not have the same widespread VTE scare as the Ortho Evra patch did in the US.

## New patches EE/GSD

A novel transparent patch has been developed by Bayer that delivers 0.5 mg EE and 2.1 mg gestodene (GSD). GSD is a progestin contained in many COCs widely used in Europe for years. It is a favorable drug for transdermal use as it has an established efficacy and safety profile, and good skin absorption allowing for a low dose needed and small patch size. The dosing of this 11 cm<sup>2</sup> patch results in the same amount of hormone exposure as the 0.02 mg EE and 0.06 mg GSD OC. This dosage was justified in a Phase IIa study that showed ovulation inhibition is not as effective with half the dose of estrogen or progestin.<sup>30</sup> The EE/GSD patch has decreased EE exposure measured by the AUC compared to the EE/NGMN patch.<sup>31</sup> Similar to the EE/NGMN patch, there is a 7-day application period for 3 weeks with 1 week patch-free (21/7). In a Phase III uncontrolled, open-label study, the EE/GSD patch had an unadjusted PI of 1.19 and an adjusted PI of 0.81 for pregnancy due to noncompliance. Of those originally enrolled, 14.3% discontinued due to an adverse event. Of those who stayed in the study, compliance was high with a mean of 97.9% and a median of 100%. At least one adverse event was reported in 61.7% of subjects, the most common being headache (9.5%), application site reaction (8.5%), nasopharyngitis (7.0%), cervical dysplasia including atypical squamous cells of undetermined significance (6.2%), and application site erythema (4.9%). Two of 1,631 women in the study were diagnosed with pulmonary embolism, over the course of the year of the study.<sup>32</sup>

Despite the lower EE delivery in the EE/GSD patch, bleeding patterns were shown to be similar compared to the EE/NGMN patch in a descriptive study. Withdrawal bleeding was shorter in the EE/GSD patch group in the first seven cycles with similar intensity. The incidence of breast pain was slightly lower in EE/GSD users compared to traditional EE/NGMN patch users, which is expected given the total lower estrogen exposure.<sup>33</sup> When compared to a COC containing 0.02 mg EE and 0.1 mg LNG in a Phase III double-blind, double-dummy multicenter trial, bleeding cycle and patterns were comparable.<sup>34</sup>

## EE/LNG (AG200-15)

An investigational contraceptive patch, AG200-15, has been developed by Agile Therapeutics (Princeton, NJ, USA). This patch is a 15 cm<sup>2</sup> matrix core with a surrounding adhesive

for a total area of 26 cm<sup>2</sup>, containing 2.3 mg EE and 2.6 mg levonorgestrel (LNG). Major differences between this and the currently marketed NGMN/EE patch are the decreased AUC of estrogen and the use of LNG, which has been shown to have lower rates of VTE compared to other progestins. Like the other patches, each patch was applied to the skin for 7 days three times per cycle followed by one patch-free week, for a 21/7 cycle. This dosing provides similar LNG and EE serum concentrations compared to those of 20 µg LNG and 30 µg EE pill.<sup>35</sup>

In a Phase III open-label study including obese and nonobese women, the PI for the patch was 4.45, compared to 4.02 for the 100 µg LNG, 20 µg EE pill. Compliance was determined by a self-reporting diary and verified by LNG and EE levels. After eliminating pregnancies in women with undetectable hormone levels, the PIs were 2.82 for the patch and 3.8 for the pill, which, statistically, were not significantly different. Of note, PIs in obese and nonobese patients did not significantly differ at 4.59 and 4.40, respectively. Self-reported compliance in this study was 91.6% in patch users and 79.8% in nonpatch users. However, the rates of laboratory-confirmed compliance for cycles 2 and 6 were 9.9% and 11% for the patch and 8.8% and 12.6% for the pill, which were not significantly different for the two methods. The discrepancy between self-reported and laboratory-verified compliance sheds light on prior studies that used patient diaries to assess compliance and may have been overestimating rates.<sup>36</sup> A second Phase III clinical trial of the EE/LNG patch is being conducted (NCT02158572), as the first trial including obese and nonobese women had a high PI and high noncompliance rates.

Bleeding patterns were similar in the patch and pill groups with 25.4% and 23.2% of women with unscheduled bleeding or spotting, respectively. There were similar rates of discontinuation due to bleeding for each method. A total of 21.8% of patch users experienced a drug-related treatment-emergent adverse event compared with 16% in the pill group. Most treatment-emergent adverse events were mild-to-moderate in severity. The most common adverse events were estrogen related, including nausea, headache, increased weight, and breast tenderness.<sup>34</sup> Skin reaction occurred in 3.2% of patch users, a lower rate than that seen with the traditional NGMN/EE patch.<sup>37</sup> Low detachment rates have been reported (2.0%–3.7%), with sustained wearability with exercise and in humid climates.<sup>38,39</sup>

## Conclusion

Transdermal patches provide an effective and convenient method of hormonal contraception. Its once-weekly application

is appealing for women who want an alternative to daily OCs. Although this offers a theoretical benefit of higher compliance and lower failure rates, efficacy is in the same range as oral and transvaginal CHCs.<sup>40</sup> Compliance rates are reported to be higher in patch users compared to pill users; although most studies use diaries or self-reporting to measure compliance, there may be some inaccuracy. Additionally, compliance and continuation are low in adolescents, so the failure rate with typical use may be higher in this population.

The side effect profile of the patch is similar to that of combined OCs, which are estrogen-related and mostly mild-to-moderate in severity. These include nausea, breast tenderness, emotional lability, and dysmenorrhea. One unique adverse effect is application site reaction, which occurs in ~20% of users and is treatment-limiting in 2%. Adhesion of the patch remains high in humid climates and with exercise.<sup>20</sup>

An advantage of the transdermal route is that the levels of estrogen are steady without the peaks and troughs seen with OCs, but the AUC of estrogen is higher in patch users. Given the higher total estrogen exposure, there has been concern raised over a higher risk of VTE compared to pill users. Studies are conflicting, but there is evidence that the patch confers a twofold risk of developing a nonfatal thromboembolic event compared with OCs. Although the relative risk is higher for VTE compared to OCs the absolute risk of VTE remains low. In light of this potential increased risk, two new patches with lower estrogen exposure based on AUC and different progestins are under investigation. One is a smaller, transparent EE/GSD patch being studied in Europe. The other is the EE/LNG patch in the US that has not yet received FDA approval. It will be interesting to see if there is higher uptake, acceptability and continuation with newer patches.

## Disclosure

The authors report no conflicts of interest in this work.

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