The major use of hormonal contraception is, obviously, for family planning, although hormonal contraception may be used for a variety of gynecologic reasons, for example cycle regulation, menorrhagia and related anemia, premenstrual symptoms, endometriosis, acne, endometrial hyperstimulation and ovarian cysts. However, these additional uses will not be reviewed here. Approximately 95% of sexually active women in the USA use contraception at some time [1]. However, unintended pregnancy accounts for 84 million of the 210 million estimated pregnancies that occur annually [2]. Thus, almost 50% of pregnancies in the USA are unintended, resulting in an estimated US$5 billion in healthcare costs [3]. State-sponsored Medicaid family-planning projects are estimated to have saved California (USA) US$2.2 billion over 5 years [4]. Decreasing the unintended birth rate starts with offering women a variety of contraceptive methods. For some women, the most common method of hormonal contraception, the combination oral contraceptive, is not an option for a variety of reasons, making other approaches critical. Furthermore, a significant proportion of unintended pregnancies occur among women who were using an oral contraceptive [2]. Therefore, a combined hormonal contraceptive product with a longer dosing frequency may offer advantages relative to compliance with the method.

The purpose of this article is to review data that support the use of the transdermal contraceptive patch as a method of birth control. The transdermal contraceptive patch provides a weekly dosing approach without sacrificing efficacy. The frequency of side effects is similar to that experienced by oral contraceptive users, although certain side effects, for example, breast tenderness and skin irritation, are more common among patch users. Although there has been concern that the transdermal contraceptive patch may be associated with higher rates of venous thromboembolism than other combination contraceptive methods, study results are not consistent, and the rates of venous thromboembolism are significantly lower than those experienced by pregnant women.

**Keywords:** combination hormonal contraception • ethinyl estradiol • Eva™ • norelgestromin • Ortho Eva™ • transdermal contraceptive patch

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method with every act of intercourse, for example, spermicides or barrier methods. Options for multidaily combined hormonal contraception include the contraceptive patch and the contraceptive ring (Nuva Ring®). In addition, the implantable rod (Implanon™) containing the progestin etonogestrel, and two intrauterine contraceptive devices, the copper T 380a and the levonorgestrel-releasing system, all offer lengthy dosing frequencies but clearly place control of initiation and discontinuation of the method in the hands of the healthcare professional.

Introduction to the drug
Transdermal delivery of contraceptive steroids has a number of advantages. Transdermal delivery systems provide continuous administration of drug via the skin, which maintains relatively constant plasma drug levels, thus avoiding the peaks and troughs seen with oral contraceptives [5–7,101]. Losses of bioavailability due to first-pass hepatic metabolism and enzymatic degradation in the GI tract seen with oral drug administration are avoided, which makes it possible to use lower doses of steroids to achieve contraceptive efficacy [8,9]. Other advantages of transdermal patches include a nonoral route of administration for women who are unable to take oral medications and immediate cessation of steroid administration with removal of the patch [5].

The first transdermal contraceptive patch, a matrix system containing a combination of norelgestromin and EE (Ortho Evra), was approved by the US FDA in November 2001. 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 constant, continuous levels of hormones [10–13].

The contraceptive transdermal patch is a rectangular patch that is 20 cm², approximately the size of a matchbook, with an outer protective layer, a medicated adhesive layer in the middle and a clear liner that is removed at the time of skin application [11]. The medicated layer contains 0.75 mg of EE as the estrogen component of the system. Estrogens in combination hormonal contraceptives suppress follicle-stimulating hormone, preventing the occurrence of a dominant follicle, stabilize the endometrium to reduce unintended bleeding and potentiate the action of progesterational agents. Norelgestromin, formerly known as 17-deacetyl-norgestimate (the primary metabolite of noregestimate) provides the progestin component. A total of 6.0 mg of this progestin is contained in each patch. Progestational agents serve to suppress luteinizing hormone to prevent ovulation, thicken the cervical mucus to impair sperm transport and make the endometrium less receptive to implantation of a fertilized ovum. When applied to the skin, the system delivers EE 20 µg/day and norelgestromin 150 µg/day. The medicated adhesive layer contains enough of the steroid components to last for 9 days, although weekly changing is recommended.

Pharmacokinetics & metabolism
During the 7-day wear period, the patch delivers constant, continuous levels of hormones and avoids the peaks and troughs seen with oral contraceptives. Both EE and norelgestromin reach steady-state conditions over three cycles of treatment, and mean serum concentrations for both hormones remain within the serum levels required to be effective [11]. However, the AUC and average concentration at steady state for EE is approximately 60% higher in women using the transdermal contraceptive patch compared with women using an oral contraceptive containing EE 35 µg [10]. However, peak concentrations for EE are approximately 25% higher in oral contraceptive users compared with patch users.

Other differences in the biological effects of the patch when compared with oral contraceptive users include less follicular development and a lower incidence of presumptive ovulation (based on serum progesterone ≥ 3 ng/ml) [12]. The patch’s effects on androgenic markers are comparable to that of most oral contraceptives [13].

Clinical efficacy
Three trials were initially conducted to determine the efficacy of the contraceptive patch. Hedon et al. randomized 1517 subjects: 861 subjects received the contraceptive patch and the remaining women an oral contraceptive containing EE 20 µg and desogestrel 150 µg [14]. A third of subjects used the method for 13 cycles, and the remainder for six cycles. Pearl indices for overall and method failures for the patch were 0.88 and 0.66, respectively, and for the oral contraceptive were 0.56 and 0.28, respectively. The differences between the contraceptive patch and oral contraceptive were not statistically significant. There were three method-failure pregnancies on the contraceptive patch, with a cumulative probability of pregnancy of 0.5% at 13 cycles.

Audet and coworkers randomized 1417 subjects: 811 subjects received the contraceptive patch and the remainder received a triphasic oral contraceptive containing EE 30/40/30 µg and levonorgestrel 50/75/125 µg [15]. A third of subjects used the method for 13 cycles and the remainder for six cycles. Pearl indices of overall and method failure for the patch group were 1.24 and 0.99, respectively, and 2.18 and 1.25, respectively in the oral contraceptive group. These differences between patch and oral contraceptive users were not statistically significant. There were four method-failure pregnancies and one user-failure pregnancy during 5240 cycles of patch use. The cumulative probability of pregnancy for contraceptive patch users was 0.6% at six cycles, and 1.3% at 13 cycles.

Smallwood and coworkers conducted an open-label, single-arm, multicenter, clinical trial that included 501 subjects who received 13 cycles of treatment and 1171 subjects who received six cycles of treatment [16]. Overall and method-failure probabilities of pregnancy were 0.4 and 0.4% through six cycles, and overall and method-failure probabilities of pregnancy were 0.7 and 0.4% through 13 cycles. There were five method-failure pregnancies and one user-failure pregnancy during 10,994 cycles of patch use. For contraceptive patch users, the overall Pearl index was 0.71, and the method-failure Pearl index was 0.59.

In Europe and South Africa, 65 centers participated in a randomized, comparative trial of 1489 women comparing the contraceptive patch to multiple oral contraceptive formulations [17]. In this trial, 846 subjects used the patch and 643 used an oral contraceptive for six or 13 cycles. The overall and method-failure probabilities...
of pregnancy for patch and oral contraceptive users were 0.5 and 0.4%, respectively, through 13 cycles, and 0.5 and 0.4%, respectively, through six cycles. The overall and method-failure Pearl indices for the patch were 0.88 and 0.66, respectively. For users of oral contraceptives, the Pearl indices for overall and method failures were 0.56 and 0.28, indices that were not statistically significantly different from those of patch users.

Finally, in the pooled analysis of the original efficacy trials for the contraceptive patch [15-17], a significant association between greater baseline bodyweight and pregnancy was found (p < 0.001) [18]. Five out of 15 on-treatment pregnancies occurred in the subgroup of women with a baseline bodyweight greater than or equal to 90 kg (≥198 lb). For women below 90 kg, no association between bodyweight and pregnancy was found. However, these findings need to be interpreted with caution since they were based on a very small sample size, were not adjusted for possible confounders and were in studies that were not designed to examine this particular issue.

Safety & tolerability
As with other combined hormonal contraceptive methods, the major risks potentially associated with the contraceptive patch are venous thromboembolism (VTE), myocardial infarction (MI) and stroke.

Venous thromboembolism
Based on a number of passive consumer reports regarding possible VTE related to transdermal contraceptive patch use, the manufacturer with concurrence of the FDA-sponsored studies to examine this issue. Two separate case–control epidemiological studies evaluated the risk of VTE, as well as MI and stroke in contraceptive patch users compared with women using a norgestimate-containing EE 35 µg oral contraceptive [19,20]. Jick examined the risk of nonfatal VTE in a nested case–control study using data from Pharmetrics, a US company that collects insurance claims information from managed care plans [19]. The study identified 68 cases of VTE in women aged 15–44 years; 31 among contraceptive patch users and 37 among users of the oral contraceptive. In this study, 266 control subjects (women without VTE) were matched by year of birth and index date of the case in a ratio of approximately 4:1. The odds ratio of nonfatal VTE comparing the patch to the oral contraceptive was 0.9 (95% CI: 0.5–1.6). The overall incidence rate for VTE was 52.8 per 100,000 women-years (95% CI: 35.8–74.9) among patch users and 41.8 per 100,000 women-years (95% CI: 29.4–57.6) for users of the norgestimate-containing oral contraceptive. This study indicated that the risk of nonfatal VTE among transdermal contraceptive patch users is similar to that of users of oral contraceptives containing 35 µg of EE and norgestimate [19].

A second nested case–control study was conducted by i3 Drug Safety, an Ingenix company (MN, USA), using insurance claims information from the Ingenix database, as well as medical record verification of the VTE, MI and stroke cases [20]. The objectives of this study were to evaluate the combined risk of heart attack and stroke in users of the contraceptive patch compared with users of norgestimate-containing oral contraceptives with EE 35 µg, as well as to separately evaluate the risk of heart attack, stroke and VTE in these same women. For VTE, there were 61 total cases, of which 22 were among contraceptive patch users and 39 were among users of norgestimate-containing oral contraceptives; 57 and 186 control women without evidence of VTE were matched to the cases by date of birth and index date in each treatment group, respectively. The odds ratio for VTE comparing current users of the patch to current users of oral contraceptives was 2.42 (95% CI: 1.07–5.46) [20]. The estimated incidence of VTE per 100,000 women-years was 40.8 for contraceptive patch users and 18.3 for users of the norgestimate-containing oral contraceptive. Although these data differ from the Jick study; it should be noted that VTE is relatively rare and has been reported as a potential risk of all combination hormonal contraceptive therapy. There is also concern that combination hormonal products containing the progestin norgestimate or its derivative norelgestromin may, in some fashion, enhance the thrombogenic effects of EE. However, available data do not support this conclusion. In a cohort study from a claims paid database, the incidence of VTE per 100,000 woman-years for women using combination oral contraceptives containing norgestimate, desogestrel or levonorgestrel were 30.6, 53.5 and 27.1, respectively [21]. The level of difference in VTE risk reported in the i3 Drug Safety study is quite similar to that reported in this study. Finally, this risk is even less than that reported for a new oral contraceptive containing the progestin drospirenone [22]. Although the overall rates of VTE among combination hormonal contraceptive users in these studies appear higher than those reported previously, it should also be noted that the absolute risk of symptomatic VTE in pregnancy ranges from 50 to 300 events per 100,000 pregnancies, rates that are also higher than previously reported [23].

Stroke & myocardial infarction
Jick and colleagues also utilized their same database to evaluate the risk of stroke and MI [24]. They identified 18 women aged 19–43 years who had a first stroke (approximately 80% were thrombotic) while taking a study contraceptive. At the index date, eight women were exposed to the contraceptive patch and ten were exposed to a norgestimate-containing oral contraceptive. The crude incidence rate of ischemic stroke was 13.6 per 100,000 woman-years (95% CI: 5.9–26.8) among patch users and 11.3 per 100,000 woman-years (95% CI: 5.4–20.8) for users of norgestimate-containing oral contraceptives. The crude relative risk of ischemic stroke among patch users as compared with the oral contraceptive users was 1.2 (95% CI: 0.41–3.4). There were not enough cases in either group to adjust for age or calendar time. Although the women were current contraceptive users, several had risk factors for stroke, such as diabetes mellitus, hypertension and atrial septal defects. Nine women had no documented risk factors. Eight women aged 20–43 years were diagnosed with an acute MI. At the index date, one woman was exposed to the contraceptive patch and seven women were exposed to a norgestimate oral contraceptive. The crude incidence rate of acute MI among current patch users and norgestimate-containing oral contraceptives
was 1.7 per 100,000 woman-years (95% CI: 0.04–9.5) and 7.9 per 100,000 woman-years (95% CI: 3.2–16.3), respectively. The crude relative risk of MI among patch users compared with oral contraceptive users was 0.2 (95% CI: 0.004–1.7). Four women had one or more risk factors for MI, such as diabetes, hypertension, hyperlipidemia or obesity. It was concluded that the data did not support an increased risk of ischemic stroke or acute MI among users of the patch compared with users of a norgestimate-containing oral contraceptive. Most importantly, it should be noted that such events are quite rare among young women who use combination hormonal contraceptives and who do not have significant risk factors.

**Breakthrough bleeding & spotting**

Breakthrough bleeding (BTB) and spotting with the patch has been comparable to or less than that seen with oral contraceptives. For example, in a comparative trial, subjects utilizing the contraceptive patch had less BTB than the subjects using the comparator oral contraceptive, which contained EE 35 µg and norgestimate 250 µg [25]. In another comparative study, there were no statistically significant differences between users of the contraceptive patch and users of a triphasic oral contraceptive containing EE 30/40/30 µg and levonorgestrel 50/75/125 µg with respect to BTB during any cycle [17]. In a single-arm study, the rate of BTB among patch users at 13 cycles was 1.7% and the rate of all unscheduled bleeding (BTB or spotting) at 13 cycles was 9.2% [16]. In a European and South African study, rates of BTB during cycle three were 14% in the patch group and 15% in the oral contraceptive group; at cycle 13, the BTB rates were 8.2 and 12.0%, respectively [26].

**Breast tenderness**

Breast tenderness, conversely, is more common among patch users in the initial months of use. For example, in one comparative study of 13 cycles in length, the overall occurrence was higher for patch users than oral contraceptive users, although the difference was significant only in cycles one and two; 15.4 versus 3.5% in cycle one (p = 0.001) and 6.6 versus 1.5% in cycle two (p = 0.001) [18]. In total, 85% of subjects rated the discomfort as mild-to-moderate in severity. Hedon and Urdl also noted that the overall rate of breast tenderness was higher for patch users than for oral contraceptive users (19% for the patch, 6% for oral contraceptive users and 25.1% for the patch, 8.9% for oral contraceptive users, respectively) [14,17]. The Urdl study also found that breast tenderness was treatment limiting for 3.0% of contraceptive patch users and 0.2% of oral contraceptive users.

**Application-site reactions**

Mild-to-moderate and transient application-site reactions have also been reported. In two of the initial trials, the incidence ranged from 6.7 to 13.8% of subjects, with the reaction being treatment limiting for 1.2% of subjects [17,25]. However, another study noted rates of skin reaction of 33.7% at cycle one declining to 14.7% by cycle nine. In this study, site reaction was treatment limiting for 5.6% of subjects [26].

**Headache, nausea & dysmenorrhea**

In one of the comparative trials, other common side effects were similar for contraceptive patch and oral contraceptive users [26]. For example, for patch users versus oral contraceptive users, the rate of headache was 21.9 and 22.1%, respectively, the rate of nausea was 20.4 and 18.3%, respectively, and dysmenorrhea was 13.3 and 9.6%, respectively.

**Extended use**

Extended use with the contraceptive patch was studied to compare bleeding profiles and satisfaction to women using the patch in the conventional fashion [27]. A total of 229 healthy, menstruating women were randomly assigned: 158 women to receive the transdermal patch in an extended regimen (weekly application for 12 consecutive weeks, one patch-free week and three more consecutive weekly applications) and 81 women to utilize the conventional cyclic regimen (four consecutive cycles of three weekly applications and one patch-free week). Extended use of the transdermal contraceptive patch resulted in fewer median bleeding days (six compared with 14; p < 0.001), bleeding episodes (one compared with three; p < 0.001), and bleeding or spotting episodes (two compared with three; p < 0.001) compared with cyclic use during days 1–84. The overall median numbers of bleeding or spotting days were similar between regimens (14 compared with 16) during the same period.

**Regulatory affairs**

Since being approved by the FDA, prescribing information for Ortho Evra has been has modified several times [102]. In November 2005, a bolded warning was issued that women using Ortho Evra were exposed to higher doses of estrogen that potentially could increase their risk for serious side effects. This warning was based on pharmacokinetic data described previously that demonstrated that the AUC for EE in the patch was 60% higher over one month than an oral contraceptive containing EE 35 µg [10]. Of note, the peak levels of EE were 25% higher in the oral contraceptive users than the patch users. In 2006, additional nonbolded warnings related to VTE were issued, indicating that users of the patch may face increased risk of VTE. In addition, there was a description of the two nested case–control studies discussed previously in this paper [19,20].

Internationally, the transdermal contraceptive marketed as Evra™, was approved by the European Medicines Regulatory Agency and the UK Regulatory Department in 2003.

**Conclusion**

The contraceptive transdermal patch delivers EE 20 µg/day and norelgestromin 150 µg/day with a weekly dosing frequency for 3 weeks followed by a 1-week hormone-free interval. In clinical trials, this method has an efficacy and rate of side effects similar to that of combination oral contraceptives. However, the type of side effects varies somewhat, with breast tenderness and skin irritability being more common among contraceptive patch users. The potential for an increased rate of VTE due to its pharmacokinetic profile has led to additional product labeling and for two
case–control studies to be conducted to evaluate this issue. One study showed no difference in risk and one showed approximately a twofold increase of risk of VTE when the contraceptive transdermal patch was compared with an oral contraceptive containing the same hormones. Furthermore, the estimated rates of this complication were lower than those experienced by women who are pregnant or postpartum.

**Five-year view**
The future for transdermal contraception remains cautiously optimistic. Possibilities include more widespread extended usage, multiple dosing and cosmetically optimal dispensing media. It should be noted that, at least in the USA, the publicity surrounding the possibility of increased rates of VTE with use of the current patch coupled with the revised package insert has negatively affected prescribing patterns and may also decrease interest in developing modifications of the current patch. For example, marketing data in the USA indicates that, although there have been an estimated 6,778,000 new-start users of the transdermal patch between its introduction in April 2002 and August 2008, the number of new-start users per year has fallen from a peak of approximately 1,732,000 in 2004 to approximately 238,000 new starts in 2007 [28]. However, should a new or modified transdermal system be developed without these limitations, use of transdermal contraception may increase.

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**Key issues**
- Contraception remains an important aspect of healthcare for women.
- Unintended pregnancy continues to be a significant problem, despite multiple advances in contraception.
- Use of the transdermal contraceptive patch provides a unique delivery system that also reduces the frequency of dosing to three-times per month.
- The contraceptive patch has efficacy rates and rates of side effects similar to those experienced by combination oral contraceptive users.
- Concern about risk of venous thromboembolism has led to additional labeling, although the available data is not consistent.

Furthermore, the rate of this complication is less than that experienced by pregnant and postpartum women.

**References**
Papers of special note have been highlighted as:
• of interest
** of considerable interest
• One of the initial studies examining the efficacy and side effects of the transdermal contraceptive patch.
• One of the initial studies examining the efficacy and side effects of the transdermal contraceptive patch.
Drug Profile
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- One of the initial studies examining the efficacy and side effects of the transdermal contraceptive patch.


- One of the two case–control studies of the risk of thromboembolism with the transdermal contraceptive patch.


- One of the two case–control studies of the risk of thromboembolism with the transdermal contraceptive patch.


- Only published study examining extended use of the transdermal contraceptive patch.

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**Websites**


102 US Food and Drug Administration www.fda.gov

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