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# Issues in Emerging Health Technologies

# Transdermal Contraceptive Patch - a new birth control option

## Summary


- ✓ **A new, once-weekly contraceptive patch (Ortho Evra™) that delivers transdermally norelgestromin and ethinyl estradiol was approved by the U.S. FDA November, 2001.**
- ✓ **Patch drug delivery systems theoretically offer advantages over oral therapy, including enhanced adherence to treatment regimen and reduction in adverse events.**
  - **A randomized controlled trial (RCT) demonstrated better adherence to the treatment regimen, with the patch when compared to an oral contraceptive (OC).**
  - **However withdrawals due to adverse events and participant choice were higher in patch users than in OC users.**
- ✓ **An RCT covering six or 13 menstrual cycles indicated that the short-term efficacy of the patch was similar to that of the OC, but the risk of pregnancy in the long term is not known.**


## The Technology

The transdermal contraceptive patch is a new method of delivering combination hormonal contraception. The mechanism of action of this patch is similar to that of oral contraceptives (OCs), which act by suppressing ovulation, changing cervical mucus (which hinders sperm migration through the endocervix), and altering the endometrium (which makes implantation of the embryo difficult).[1,2] Ortho Evra™, is a patch designed to deliver transdermally, continuous levels of norelgestromin (progestin) and ethinyl estradiol (estrogen) for a seven-day period.[3] Norelgestromin is the primary active metabolite of norgestimate, a progestin frequently used in oral contraceptives.[3] The patch is 20 $cm^2$ in size, thin and comprised of three 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.[4]

## Regulatory Status

The contraceptive patch, Ortho Evra™, developed by the R.W. Johnson Pharmaceutical Research Institute, was approved by the United States (U.S.) Food and Drug Administration November, 2001.[5] As of October 2001 there is no information available on the regulatory status of the contraceptive patch in Canada.

## Patient Group

Contraception enables women to prevent unintended pregnancies. In Canada, an estimated 1.3 million women aged 15 to 49 reported using OCs in 1996/97.[6] Accidental pregnancies occur in 5% of typical users and in less than 1% of users who consistently and correctly take OCs for one year.[7] Improper usage of OCs is associated with a lack of established routine for pill taking, lack of adequate information and occurrence of certain side effects, including nausea, bleeding irregularities, breast tenderness and hirsutism.[8] The transdermal contraceptive patch was designed to deliver a combination of hormones (similar to that found in OCs) and to achieve better user adherence to therapy.

## Current Practice

A number of different methods of contraception, both reversible and non-reversible are currently available.[1]

**Reversible methods:**

1. Oral contraceptives are either a combination of estrogen and progestin or progestin alone.[9]
2. Injectable contraceptives (e.g. Depo-Provera) contain a combination of estrogen and progestin or progestin alone and are injected every one to three months.[9,10]
3. Hormone implants (e.g. Norplant, which is surgically implanted in the arm) allow the sustained-release of progestin and can be used for contraception for one to five years.[9,11]
4. Intrauterine devices (e.g. Nova-T, Gyne-T) provide contraception for one to 10 years, depending on the type of device.[7,12]
5. Barrier methods include condoms, the diaphragm and cervical cap and the contraceptive sponge.[1,13]
6. Spermicides are available as foams, creams, gels, vaginal suppositories and vaginal films.[13]

**Irreversible method:**
Sterilization involves surgical interruption of the fallopian tubes in women or the vas deferens in men to prevent fertilization. [1,12]

## Administration and Cost

The contraceptive patch (Ortho Evra™) needs to be worn for one week at a time and to be changed the same day of the week three times a month, with the fourth week being patch free. The patch can be applied to various areas of a woman's body - the buttocks, lower abdomen, upper outer arm or upper torso (excluding the breast).[3,4] The patch can be worn during swimming, bathing and exercising.[14] The patch appears to be less effective in women weighing more than 198 lbs.[5] The risks of using this product are similar to the risks of using OCs, including an increased risk of blood clots, heart attack and stroke.[5] As of October 2001, no information is available regarding the cost for this method of birth control.

## Rate of Technology Diffusion

It is difficult to estimate the rate of diffusion of the patch since its cost and its long-term contraceptive effectiveness with respect to other methods are not known. However, contraceptive users who find daily dosing tedious, may consider the patch an attractive option.

## Concurrent Developments

A contraceptive patch developed by Agile Therapeutics is currently being examined in clinical trials in the U.S. and internationally.[15] It is a seven-day transdermal contraceptive delivery system in the form of a patch, designed to deliver a combination of levonorgestrel (LNG) and ethinyl estradiol (EE).[15] Three different patch sizes (7.5, 10 and 12.5 $cm^2$) have been investigated and have demonstrated serum LNG and EE levels similar to low dose oral LNG/EE administration.[15]

A once-weekly patch formulation containing gestodene 75 μg and ethinyl estradiol 25 μg is under development at Schering AG and is currently in Phase II trials.[16]

## The Evidence

A multi-centre, open-label RCT, supported by the R.W. Johnson Pharmaceutical Research Institute, was conducted from October 1997 to June 1999, with 1,417 healthy women aged 18 to 45, to compare the contraceptive patch with an OC.[4] One treatment arm (n = 812) received the Ortho Evra™ patch (designed to deliver norelgestromin 150 μg and EE 20 μg daily; applied weekly for three consecutive weeks followed by one patch-free week). The other treatment arm (n = 605) received an OC (Triphasil, LNG 50 μg and EE 30 μg days 1-6, LNG 75 μg and EE 40 μg days 7-11, LNG 125 μg and EE 30 μg days 12-21, and placebo for days 22-28; Wyeth-Ayerst Laboratories). In the patch group, 559 and 253 women were treated for six and 13 cycles respectively and in the OC group the corresponding numbers of women were 412 and 193. Demographic characteristics (mean age, height and weight; race and previous oral contraceptive use) were similar in the two groups.

**Contraceptive efficacy:** The contraceptive efficacy was determined using the Pearl Index (number of pregnancies per 100 person-years of use) and the cumulative probability of pregnancy. There were no statistically significant differences in pregnancy rates between the patch group and the OC group, as indicated by the overlapping 95% confidence intervals (CI) seen in Table 1. Approximately one third of the participants were studied for 13 cycles, the remainder being studied only for six cycles.

**Table 1: Contraceptive efficacy.**

| Outcome Measured | Treatment Group Value (95% CI) [n]+ Patch | OC |
|---|---|---|
| ***Pearl Index*** | | |
| - Overall | 1.24 (0.15-2.33) [811] | 2.18 (0.57-3.80) [605] |
| ***Cumulative probability of pregnancy**** | | |
| - Overall, 6 cycles | 0.6 (0.0-1.2) [559] | 1.2 (0.2-2.1) [412] |
| - Overall, 6 & 13 cycles | 1.3(0.0-2.7) [811] | 1.8 (0.2-3.4) [605] |

+ n = number of participants

* Kaplan-Meier estimates of the cumulative probabilities of pregnancy

**Cycle control:** Compared to the OC, the patch group had significantly higher bleeding and/or spotting in the first two cycles but these events were similar between the two groups for subsequent cycles. Amenorrhea (absence of any menstrual bleeding) occurred in 0.1% of the patch group and 0.2% of the OC group.

**Compliance (adherence to therapy):** Better user compliance was achieved with the patch. The mean proportion of each participant's cycle that showed compliance was 88.2% for the patch and 77.7% for OC ($p < 0.001$). Another RCT with 643 patients showed compliance of 94.4% with the patch and 87.8% with the OC (Mercilon: desogestrel 150 ：g/ EE 20 ：g).[17]

**Adverse events:** The most common adverse events experienced by both the patch and OC users are shown in Table 2.

Compared to the OC group, the patch group had a higher percentage of withdrawals but a lower percentage lost to follow-up (Table 3).

**Table 3: Withdrawals and lost to follow-up**

| | Percentage of participants | | p value |
|---|---|---|---|
| | Patch group n=812 | OC group n=605 | |
| ***Withdrawal due to:*** | | | |
| - adverse events | 12.0 | 5.0 | |
| - serious adverse events | 0.6 | 0.5 | |
| - participant choice | 9.5 | 6.6 | |
| - all of the above reasons combined | 22.0 | 12.1 | <0.0001 |
| ***Lost to follow-up*** | 3.9 | 7.9 | 0.0016 |

There were no clinically meaningful changes in most laboratory parameters, vital signs, or physical and gynaecologic examination findings in the two treatment groups. However, increases in total cholesterol and triglyceride levels were significantly higher in the patch group compared to the OC group (Table 4).

**Table 4: Changes in cholesterol and triglyceride levels**

| | Patch group | OC group | p value |
|---|---|---|---|
| ***Increase in:*** | | | |
| - total cholesterol (mmol/L) | 0.41 | 0.21 | <0.001 |
| - triglyceride (mmol/L) | 0.11 | 0.01 | 0.008 |

**Table 2: Most common adverse events**

| Adverse events | Overall incidence (%) | | p value | Treatment limiting+ incidence (%) | | p value |
|---|---|---|---|---|---|---|
| | Patch group n=812 | OC group n=605 | | Patch group n=812 | OC group n=605 | |
| Headache | 21.9 | 22.1 | 0.95 | 1.5 | 0.3 | 0.03 |
| Nausea | 20.4 | 18.3 | 0.34 | 1.8 | 0.8 | 0.12 |
| Application site reaction | 20.2 | NA* | NA* | 2.6 | NA* | NA* |
| Breast discomfort | 18.7 | 5.8 | <0.001 | 1.0 | 0.2 | 0.09 |
| Upper respiratory tract infection | 13.3 | 17.9 | 0.02 | 0 | 0 | NA* |
| Dysmenorrhea (menstrual cramps) | 13.3 | 9.6 | 0.04 | 1.5 | 0.2 | 0.01 |
| Abdominal pain | 8.1 | 8.4 | 0.85 | 0.2 | 0.3 | >0.99 |

+ discontinued treatment due to adverse events

* NA = Not Applicable

## Implementation Issues

Patch drug delivery systems theoretically offer advantages over oral therapy, including enhanced adherence to treatment. The Ortho Evra™ patch must be applied weekly whereas the OC must be taken daily. Significantly better adherence to therapy and a similar contraceptive efficacy were obtained with the patch when compared with the OC (Triphasil). It should be noted however that the study was not designed to detect differences in efficacy. Approximately one third of the participants were studied for 13 cycles, the remainder being studied only for six cycles. Therefore the risk of pregnancy in the long term is not known.

A higher rate of adherence to therapy with the patch, however, does not indicate greater user satisfaction overall, since the withdrawal rate was higher with the patch group than in the OC group. The relative impact of increased adherence to therapy and increased discontinuation due to side effects, on the overall effectiveness is yet to be determined.

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This brief was prepared by
Srabani Banerjee, M.Sc., Ph.D.;
CCOHTA
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