# The Study of Cycle Control, Side Effects and Acceptability of Transdermal Patch Use in Thai Women in Siriraj Hospital

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## ABSTRACT

**Objective:** To evaluate the efficacy, cycle control of menstruation, side effects, and acceptability of the contraceptive patch in Thai women.

**Methods:** In this noncomparative study, 60 healthy Thai women were treated with contraceptive patches. Assessments of the efficacy, cycle control, side effects, and acceptability were performed at baseline, cycles 1, 3 and 6.

**Results:** The mean age of the participants was 25.8 years. A total of 50 women completed 6 cycles providing 300 woman-months of use, with the women who withdrew from the study providing a further 5 woman-months of use for a total of 305 woman-months. There were no pregnancies during the study, neither method nor participant failures. Withdrawal bleeding was regular and predictable, with a low incidence of unscheduled bleeding. The most frequent adverse event was breast tenderness, headache, skin irritation, hair loss, nausea, and acne. Most of the users were satisfied with the contraceptive patch.

**Conclusion:** The contraceptive patch provided effective contraception with excellent cycle control, and was well tolerated with good compliance. This convenient approach to contraception appears highly acceptable in Thai women.

**Keywords:** Acceptability, contraceptive patch, cycle control, side effects

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Hormonal contraception has been widely used since 1960. Nowadays, more than 100 million women use hormones for contraception.[1] There are a variety of hormonal contraceptives including oral, injectable, and implantable forms. However, combined oral contraceptives (COCs) represent the most prevalent hormonal contraceptive method in Thailand and other countries. A survey of contraception among Thai reproductive age women found that oral contraception is the most popular for birth prevention. Their reasons for using COCs were easy to use, convenient, easy to buy and effectiveness of birth control.[2] In addition, the safety of oral contraceptive pills for most women is now well documented.[3] With those advantages of COCs, mostly healthy women use them preventing pregnancy for long periods of time. However, oral contraceptive pills have a failure rate as high as 7.6 percent because most women using them have poor compliance and inconsistently take their pill.[4] New contraceptive methods, therefore, have been invented for increasing their efficacy and improved compliance.

The contraceptive patch was first developed in 1980.[5] The FDA (The United States Food and Drug Administration) approved the transdermal combination hormonal contraception for birth control in November 2001. It has been widely used in the USA since 2003. The contraceptive patch contains estrogen name ethynyl estradiol (EE) 600 µg, which is absorbed in blood level about 20 µg. and progestin name norelgestromin (NGMN) 6 mg, the primary active metabolite of norgestimate which is absorbed in blood level 150 µg. The contraceptive patch is a 20 $cm^2$ in size and consists of a thin, matrix type system with 3 layers and delives a high enough hormonal level for contraception. The contraceptive patch is to be applied on the dry, clean,

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healthy skin on the buttock, upper outer arm, abdomen or upper torso except the breast area on the first day of the menstrual cycle (Day 1). A new patch is applied every week for three weeks and then wears off on the 4th week for a withdrawal bleed (period).[5,6]

Now, the contraceptive patch has received regulatory approval in Thailand and has been used for contraception in Thai women. Since it is quite a new contraceptive method, it should be studied in all aspects. In Thailand, there are many studies in contraceptive patch; however, there is no study about acceptability in Thai women.[7-9] The purpose of this study is to examine the cycle control of menstruation, side effects, and acceptability of the contraceptive patch in Thai women.

## MATERIALS AND METHODS

### Study population

This study was an open-label, prospective, descriptive clinical trial performed at the family planning clinic of Siriraj Hospital, Bangkok, Thailand. The study protocol was approved by the Ethics Committee of the Faculty of Medicine Siriraj Hospital.

After January 2006, a total of 60 healthy consecutive Thai women who desired birth control at Siriraj Reproductive Health Research Center, family planning clinic, Siriraj Hospital were enrolled in the protocol, and received the contraceptive patch as their only method of contraception and follow up for six consecutive menstrual cycles.

Eligible participants were women between 18 and 40 years of age, in good physical and mental condition, with regular menstrual cycles, sexually active, willing and wished to use a transdermal patch for contraception for at least 6 consecutive cycles, and had not taken any oral contraceptive pill within 3 months or contraceptive hormonal injection within 6 months before the trial. If woman used contraceptive implantation or intrauterine device, she would have to stop and wait at least 2 menstrual cycles before starting the patch. Any woman who had given birth or had an abortion had to have menstruation for at least 2 cycles before the study.

A woman could not participate if she was suspected or currently pregnant, or breast feeding, BMI > 29 Kg/m$^2$, if she had contraindications to steroid hormonal therapy and diseases (WHO category 3, 4) such as: diabetic mellitus, hypertension or blood pressure > 140/90 mmHg, abnormal cervical cytology or suspected cervical cancer, presence of thrombo-embolism or thrombosis disorders, cardiovascular disease, recent liver disease, breast cancer, or undiagnosed vaginal bleeding. All women had to give written informed consent. Subjects received 3 transdermal patches each for 7 days, the first patch was applied during the first day of menstruation, the new patch was applied each week until 3 three consecutive weeks, and then followed by a 7-day patch-free interval for withdrawal bleeding. After completing the four-week contraceptive cycle, the next cycle was started by applying a new patch. The participant was assigned to receive 6 cycles of transdermal patch.

Assessments were performed at baseline and at treatment cycles 1, 3 and 6. Bleeding data, dysmenorrhea and premenstrual syndrome were assessed using diary cards. At screening at baseline, medical and gynecologic histories of all subjects were obtained, and they underwent a general physical examination, including a pelvic examination with cervical cytology sampling. At all study visits, blood pressure, heart rate, and body weight were measured. In addition, subjects were questioned on the use of any concomitant medication.

Contraceptive efficacy which was assessed by determining the occurrence of pregnancy during the study was estimated by calculating the Pearl Index. The Pearl Index was defined as the number of pregnancies per 100 woman-years of exposure.

Cycle control was assessed daily by the participants using menstrual diary cards. Bleeding items recorded were spotting (S), which was defined as bleeding, not requiring sanitary protection occurring outside the period of withdrawal bleeding, breakthrough bleeding (BTB) which was defined as bleeding heavy enough to require sanitary protection occurring outside the withdrawal bleeding period, bleeding during patch use, which was defined as either breakthrough, spotting, or breakthrough plus spotting for each cycle. The occurrence of adverse events and side effects was assessed and recorded at every study visit. In addition, any events considered directly related to patch use, such as skin irritation or device-related events (patch detachment) were recorded at each assessment during the study. The user's acceptability was assessed by questionnaires, which were completed by the subjects themselves at cycles 1, 3, and 6.

### Data analysis

The demographic data was analyzed by mean and standard deviation. Cycle control statistical analysis was performed by Computer program SPSS for Microsoft Windows version 10.0 (Chicago, IL). The level of significance was set at $p<0.05$. The results were presented as mean and standard deviation (mean ± SD).

## RESULTS

A total of 60 women were enrolled; demographic characteristics at the baseline for participants are summarized in Table 1. Of these, 50 (83.3%) completed the trial. The mean age of the participants was 25.8 years. The mean body mass index was 20.8 kg/m$^2$. Ten women withdrew from the study for a variety of reasons: Personal reason (two), adverse event (four), medical reason (one) and lost to follow-up (three). A total of 50 women completed 6 cycles providing 300 woman-months of use, with the women who withdrew from the study providing a further 5 woman-months of use for a total of 305 woman-months. There were no pregnancies

**TABLE 1.** Demographic data.

| Characteristics | Value |
|---|---|
| Mean age (years), mean ± SD | 25.8 ± 5.3 |
| Parity, n (%) | |
| 0 | 21 (33.9%) |
| 1 | 34 (57.6%) |
| >2 | 5 (8.5%) |
| Smoking, n (%) | 3 (5%) |
| Alcoholic ingestion, n (%) | 11 (18.3%) |
| Menstrual history, n (%) | |
| Regular menstruation | |
| With regular interval | 42 (70%) |
| With irregular interval | 18 (30%) |

during the study, neither method nor participant failures. Based on these data, the Pearl Index of 0.0 was calculated for treatment.

### Body weight, BMI and blood pressure

There was no significant rise in the mean body weight of the group from 51.4 kg on admission into the study to 52 kg at the end. In the same way, BMI was not changed significantly in this study. Neither mean systolic blood pressure (SBP) nor diastolic blood pressure (DBP) changed significantly during the study. More details are presented in Table 2.

### Cycle control and bleeding pattern

There was a significant decrease in cycle length of the group from 34.2 days before entry to the study to 27.2 days at the end of the first menstrual period patterns were generally regular and predictable for all participants during the study. The mean number of bleeding days and amounts of bleeding did not differ significantly between cycle 1 through cycle 6. The data show that the menstrual pattern especially cycle length after discontinuation was similar to before entry to the study. (Table 3)

During the period of patch use, the overall incidence of spotting, irregular or breakthrough bleeding were very low, occurred not more than 10.0% and there was no statistical significance. More details are presented in Table 4. The mean interval between patch removal and withdrawal bleeding was 2.5-3.7 days.

### Adverse events

The most frequently reported adverse events in this study were breast tenderness, headache, skin irritation, hair loss, nausea, and acne. The percentage of breast tenderness gradually decreased at each cycle when compared with the previous cycle. Other details were shown in Table 5.

Application site reaction including itching and skin rash were commonly reported (41.3% and 3.9%, respectively). Nausea and headache were also reported as 32.7% and 34.5% respectively of visits at the end of the first cycle, but the percentage of these symptoms decreased in subsequent cycles. There was no vomiting reported in this study. Hair loss occurred in 3.6% of women in the first cycle and did not differ in frequency in the subsequence cycles.

### Patch adhesion

The most common location for patch application was the abdomen (60%), followed by the buttocks (27.1%), the upper outer arm (10.1%), the back (1.9%) and the upper thigh (0.9%).

There was a low incidence of partial and complete detachment in this study (13.1% and 2% respectively) and the percentage of detachment was not changed through the study.

### Satisfaction

Participants' perceptions of the transdermal patch were shown in Table 6. During the study, most participants reported that overall they liked using the patch. The reported advantage was "The patch did not get in the way during sex", "The patch is easy to use", and "The patch made my menstrual cycles more regular than before I used it". Few participants reported

**TABLE 2.** Body weight, BMI and blood pressure change.

| | Admission | | Cycle 1 | | Cycle 3 | | Cycle 6 | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Body weight (Kg) | 51.4 | 7.1 | 51.7 | 7.3 | 51.8 | 7.5 | 52.0 | 7.4 |
| BMI (Kg/m$^2$) | 20.8 | 2.4 | 20.8 | 2.5 | 20.9+ | 2.6 | 21.3 | 3.3 |
| Blood pressure (mmHg) | | | | | | | | |
| Systolic | 103.2 | 9.7 | 102.6 | 7.3 | 102.4 | 7.3 | 100.8 | 7.3 |
| Diastolic | 68.8 | 8.2 | 68.6 | 6.2 | 68.2 | 6.1 | 67.2 | 7.2 |

**TABLE 3.** Menstrual pattern.

| Cycle | Cycle length (Days) | | Duration (Days) | | Amount (Pads) | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Median | Max | Min |
| Admission | 34.2 | 5.6 | 4.0 | 1.9 | 3 | 2 | 5 |
| 1 | 27.2 | 2.7 | 3.9 | 1.8 | 3 | 1 | 5 |
| 2 | 28.9 | 1.9 | 4.1 | 1.5 | 3 | 2 | 5 |
| 3 | 29.1 | 3.1 | 4.4 | 1.6 | 3 | 1 | 4 |
| 4 | 28.3 | 6.0 | 4.5 | 1.5 | 3 | 1 | 4 |
| 5 | 28.9 | 6.4 | 4.2 | 1.5 | 3 | 1 | 5 |
| 6 | 27.8 | 2.9 | 4.1 | 0.9 | 3 | 2 | 4 |
| Discontinuation | 33.4 | 4.5 | 4.7 | 1.5 | 2 | 2 | 5 |

**TABLE 4.** Bleeding pattern.

| Bleeding | Cycle 1 N= 55 | Cycle 2 N= 50 | Cycle 3 N= 50 | Cycle 4 N= 50 | Cycle 5 N= 50 | Cycle 6 N= 50 |
|---|---|---|---|---|---|---|
| None | 51(92.7%) | 48(96%) | 45(90%) | 49(98%) | 49(98%) | 47(94%) |
| Bleeding during patch used | 4(7.3%) | 2(4%) | 5(10%) | 1(2%) | 1(2%) | 3(6%) |
| Spotting | 1(1.8%) | 0 | 1(2%) | 0 | 1(2%) | 2(4%) |
| BTB | 2(3.7%) | 1(2%) | 4(8%) | 0 | 0 | 1(2%) |
| BTB+S | 1(1.8%) | 1(2%) | 0 | 1(2%) | 0 | 0 |

**TABLE 5.** Side effects.

| Side effect | Cycle 1 | Cycle 3 | Cycle 6 |
|---|---|---|---|
| Headache | 19(34.5%) | 15(30%) | 13(26%) |
| Hair loss | 2(3.6%) | 2(4%) | 1(2%) |
| Acne | 17(30.9%) | 10(20%) | 4(8%) |
| Vomiting | 0 | 0 | 0 |
| Nausea | 18(32.7%) | 15(30%) | 11(22%) |
| Breast tenderness | 32(58.2%) | 28(56%) | 25(50%) |
| Itching | 22(40%) | 18(36%) | 24(48%) |
| Skin rash | 1(1.8%) | 2(4%) | 3(6%) |
| Abdominal pain | 3(5.5%) | 4(8%) | 0 |

skin irritation, skin rash, acne, melasma, headache, vertigo, fatigue, hair loss or nausea/vomiting. Most participants felt that breast tenderness and itching were slightly increased during patch use. In addition, there was a slight increase in perceived improvement of menstrual cramping. At the end of cycle 6, 87.3% of participants indicated that they would (absolutely/most probably) recommend the contraceptive patch to others.

### Withdrawal of the study

Although there were 10 women (16.7%) who discontinued the study for various reasons (out of 60 subjects), only four were associated with adverse events, (Itching in two cases and skin rash in the remaining two). Two out of ten left from the study because of personal reasons; whereas, three cases were lost to follow up. In addition, the last woman had a medical reason, so she had to discontinue this study and did not receive further treatment.

## DISCUSSION

This study was designed to evaluate all aspect of contraceptive patch use such as; cycle control, side effects, acceptability and satisfaction during contraception in Thai women over 6 months of use. The advantage of the contraceptive patch was associated with progestin - norelgestromin. It is a primary active metabolite of norgestimate, and known for progestin's lack of androgenicity, low side effects and high efficacy for contraception and excellent cycle control. Although there are many studies determining the efficacy of contraceptive patch in Thai women,[7-9] most of them used Ortho Evra as contraceptive methods.[8,9] Ortho Evra, that is a contraceptive patch comprising of 0.75 mg. ethynyl estradiol and 6 mg. norelgestromin,[10] is developed for birth control in Europe, and contains higher hormonal doses than Evra, which is only sold in Thailand. However, the efficacy, bleeding pattern and side effects during contraceptive patch used in those studies are similar to our study. Furthermore, there is no study about the acceptability of contraceptive patch use in Thai women; this study reflects the satisfaction during contraceptive patch use.

### Efficacy & cycle control

As mentioned elsewhere, the contraceptive patch has demonstrated excellent efficacy in Thai women in this study. No pregnancy was reported during 6 cycles of contraceptive patch use. The result reported that it provides a reliable form of contraception with good cycle control. As in the previous study,[6] the contraceptive patch has a low incidence of breakthrough bleeding. In comparative studies, the incidence of breakthrough bleeding between the contraceptive patch and oral contraceptive pills was not significantly different.[11,12]

The cycle length in the first cycle was significantly shorter than the pretreatment cycle due to the day 1 start. However, the mean duration and amount of withdrawal bleeding were not significantly different among the cycles. There was no amenorrhea in this study. After discontinuation of the contraceptive patch, menstrual pattern especially cycle length was longer as before entry to the study.

Similarly to the previous studies,[6,13] cycle control in

**TABLE 6.** Perceptions of the Patch.

| No | Questionnaire | Cycle 1 | | Cycle 3 | | Cycle 6 | |
|---|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | Mean | SD |
| 1 | Overall like the patch | 4.0 | 0.7 | 4.2 | 0.7 | 4.2 | 0.9 |
| 2 | The patch got in the way during sex | 1.2 | 0.6 | 1.1 | 0.3 | 1.2 | 0.8 |
| 3 | The patch is easy to use | 4.2 | 0.9 | 4.4 | 0.6 | 4.5 | 0.6 |
| 4 | The patch made my menstrual cycles more regular than before I used it | 3.7 | 0.9 | 4.0 | 0.8 | 4.2 | 0.6 |
| 5 | The patch was itchy | 2.5 | 1.0 | 2.6 | 0.9 | 2.5 | 0.9 |
| 6 | The patch gave me a rash | 1.7 | 0.7 | 2.1 | 0.9 | 1.9 | 0.9 |
| 7 | The patch made my acne worse | 1.6 | 0.9 | 1.5 | 0.8 | 1.3 | 0.6 |
| 8 | The patch made my melasma worse | 1.2 | 0.5 | 1.2 | 0.6 | 1.2 | 0.6 |
| 9 | The patch made my breasts tenderness | 2.3 | 1.3 | 2.3 | 1.2 | 2.2 | 0.9 |
| 10 | The patch made my headaches worse | 1.8 | 0.9 | 1.8 | 0.9 | 1.6 | 0.8 |
| 11 | The patch made me a vertigo | 1.9 | 1.1 | 1.9 | 0.9 | 1.5 | 0.7 |
| 12 | The patch made me fatigue | 1.7 | 0.9 | 1.5 | 0.7 | 1.3 | 0.5 |
| 13 | The patch made me nausea or vomiting | 1.6 | 0.9 | 1.7 | 0.9 | 1.4 | 0.6 |
| 14 | The patch made me a hair loss | 1.5 | 0.7 | 1.6 | 1.0 | 1.3 | 0.7 |
| 15 | The patch gave me leg cramps | 1.3 | 0.5 | 1.5 | 0.7 | 1.5 | 0.7 |
| 16 | The patch made my menstrual cramps better | 2.3 | 1.2 | 2.0 | 1.1 | 2.1 | 1.0 |
| 17 | I would recommend the patch to friends | 4.6 | 0.8 | 4.6 | 0.6 | 4.7 | 0.6 |

Item 1 refers as: 1 = "hate it", 2 = "don't like it", 3 = "don't like" or "dislike", 4 ="like it", 5 = "love it"
Item 2-17 refer as: 1= "strongly disagree", 2 = "disagree", 3 = "neither agree nor disagree", 4 = "agree", 5 = "strongly agree."

this study was good in the majority of women. The incidence of breakthrough bleeding was low in all cycles. In addition, comparative study indicated that the incidence of breakthrough bleeding with the patch was similar to the oral contraceptive pills.[13]

**Body weight & blood pressure**

There was no significant change in body weight or blood pressure throughout the study. These results were similar to those reported in another study.[14]

**Adhesion**

The contraceptive patch was associated with a low rate of patch replacement because of partial or complete detachment in this study. (13.1% and 2% respectively) Patch replacement in this study was rather higher than a previous study[15] (1.8% and 2.9% respectively). This result may have been related to individual skin type, or differences in lifestyle. However, the result from the pooled clinical study showed that heat, humidity and exercise do not affect adhesion.[16,17]

There are several anatomic sites for patch application. Pharmacokinetic study indicated that efficacious hormonal concentrations are achieved regardless of the location of patch application.[16-18] In this study, abdomen and buttock were the most common sites that the participant applied the patch during the study. In contrast, hardly any patch was put on the back and thigh at the last cycle in the study. The reasons for location of patch application depend on the individual and convenience of users.

**Adverse event**

The incidence of side effects is also a major factor in determining the overall acceptability of a contraceptive method.[19] The result indicated that the contraceptive patch was well tolerated. Corresponding to the previous studies,[14,20] this study indicated the contraceptive patch related adverse events such as breast tenderness, headache, hair loss, nausea, and acne. In this study, breast tenderness was the most common side effect. Application site reaction such as itching was the second most common. In addition nausea, headache, acne and hair loss were also most common at the end of the first cycle, but these symptoms improved in subsequent cycles. The proportion of women reporting side effects especially breast tenderness in this study is somewhat higher than a previous study.[20] Similar to results from a previous study, adverse symptoms tend to resolve after the first 3 months of patch use.[13] In contrast to the previous study,[21] no case of thromboembolism was observed in this study.

**Satisfaction and acceptability**

Over all participants reported a positive impression and a good perception of the transdermal contraceptive patch. The higher adherence rate may result from the high efficacy, convenience of the patch, one-weekly dosing, general ease of use, less adverse events and good compliance. Almost all participants would recommend the contraceptive patch to others. These results are similar to the findings in other previous studies.[13,22,23]

## CONCLUSION

In conclusion, the contraceptive patch provided convenient and effective contraception with excellent cycle control. It was well tolerated, with good compliance, and was found to be highly acceptable to Thai women. This study indicates that the contraceptive patch is an alternative to other contraceptive methods especially combined oral contraceptives, avoiding the necessity of taking medication on a daily basis.

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