Research Protocol

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Research Proposal

1. Project Title (Proposal Title)

Thai: การศึกษาแผ่นแปะคุมกำเนิดชนิดฮอร์โมนรวมอิธินิลเอสตราดิออล (Ethinyl Estradiol) และนอร์เอลเจสโทรมิน (Norelgestromin) เพื่อรักษาอาการเลือดออกทางช่องคลอดผิดปกติในผู้ใช้ยาฝังคุมกำเนิด

English: Transdermal Ethinyl estradiol and Norelgestromin for treating irregular vaginal bleeding in contraceptive implants users: A Randomized, Double-Blind, Controlled Trial

2. Investigators

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3. Rationale and Background

- Contraceptive implants are highly effective semi-permanent contraceptive methods. The most common side effect is irregular bleeding (1-2), which is the main reason for discontinuation of this method (3-6).
- The exact cause of irregular bleeding is not clearly understood. One possible cause is endometrial thinning resulting from progestin suppression of Luteinizing Hormone (LH) and ovulation. Another possible cause is increased vascular permeability, which is controlled by COX-2. Under normal conditions, COX-2 is suppressed by LH, and when this suppression is disrupted by hormonal changes, it may lead to increased vascular permeability and cause bleeding (7).
- Various approaches have been proposed to reduce irregular bleeding, targeting different mechanisms such as NSAIDs, anti-fibrinolysis, anti-progestin, estrogen, and combined hormonal contraceptives (8).
- Previous studies have shown that treatment with oral combined hormonal contraceptives can reduce irregular bleeding (9-11).
- However, studies on the use of transdermal contraceptive patches for treating irregular bleeding are still limited (12).
- The combined hormonal contraceptive patch available in Thailand contains ethinylestradiol 600 micrograms and norelgestromin 6 milligrams. The Summary of Product Characteristics (SPC) recommends applying the patch to the upper torso for 7 days, then removing and applying a new patch. The daily hormone release into the bloodstream is Ethinyl Estradiol 20 micrograms and Norelgestromin 150 micrograms (13).

- Since combined hormonal contraceptive patches do not need to be changed daily, this method may be satisfactory for users who choose contraceptive implants for their long-acting properties and may be as effective as other methods in treating irregular vaginal bleeding. Additionally, studies have reported that patients using weekly contraceptive methods have significantly better compliance compared to daily contraceptive use (14,15).

4. Literature Review

- Alvarez-Sanchez et al. studied 155 Norplant users with irregular vaginal bleeding, comparing oral contraceptive Ethinyl Estradiol 50 μg + Levonogestrel 250 μg, hormone Ethinyl Estradiol 50 μg, and placebo. All medications were given for 20 days with 8 weeks follow-up. The number of bleeding days in the oral contraceptive group was significantly lower than the other two groups (16).
- Witjaksuno et al. studied 91 Norplant users with irregular vaginal bleeding, comparing 90 days before and after treatment. Users of oral contraceptive Ethinyl Estradiol 30 μg + Levonogestrel 250 μg and hormone Ethinyl Estradiol 50 μg had significantly reduced bleeding days compared to the 90 days before treatment (17).
- Guiahi et al. studied 32 Etonogestrel implant users with irregular vaginal bleeding. The proportion of users in each group reporting cessation of irregular bleeding during treatment and remaining bleeding-free at the end of treatment was 87.5% in the oral contraceptive Ethinyl Estradiol 30 μg + Levonogestrel 250 μg group and 37.5% in the placebo group, which was statistically significant (9).
- Hou et al. studied 26 Etonogestrel implant users with irregular vaginal bleeding. In the group receiving oral contraceptive

Ethinyl Estradiol 30 μg + Levonogestrel 250 μg, all subjects reported improvement in irregular vaginal bleeding (11).

- Sinthuchai et al. studied 46 Etonogestrel and Levonogestrel implant users with irregular vaginal bleeding. Treatment groups were divided into injectable contraceptive Estradiol cypionate 5 mg + Medroxyprogesterone acetate 25 mg compared to placebo. The proportion stopping irregular bleeding after treatment and remaining bleeding-free until 21 days post-treatment was 87% in the injectable contraceptive group, higher than placebo at 46% (18).
- Boonkasemsanti et al. studied 120 Norplant users. The group receiving transdermal hormone Oestradiol 100 μg reported clinical improvement in 23 out of 33 cases, and the placebo group reported improvement in 13 out of 31 cases. However, the comparison was not statistically significant (12).
- Audet et al. compared efficacy, cycle control, treatment compliance, and safety between transdermal combined hormonal contraceptive Ethinylestradiol 20 μg + Norelgestromin 150 μg and oral contraceptive Ethinyl Estradiol 30 μg + Levonogestrel 250 μg. Contraceptive efficacy was similar, and cycle control ability was comparable (14).

From the literature review, combined hormonal contraceptives are effective in treating irregular vaginal bleeding in contraceptive implant users. However, data on transdermal contraceptive patches for treating irregular bleeding is limited. This method has been studied to provide better user compliance, making the data from this study valuable for clinical application.

5. Research Objectives

Primary Objective:

- To evaluate the proportion of participants reporting no vaginal bleeding during treatment with combined hormonal contraceptive patches and remaining bleeding-free on day 14 of treatment

Secondary Objectives:

- To evaluate the proportion of participants reporting no vaginal bleeding after treatment with combined hormonal contraceptive patches continuously for at least 7 days in the treatment month compared to placebo (bleeding free at least 7 days)
- To evaluate the proportion of participants reporting no vaginal bleeding during treatment with combined hormonal contraceptive patches and remaining bleeding-free on day 7 of treatment
- To evaluate the proportion of participants reporting no vaginal bleeding during treatment with combined hormonal contraceptive patches and remaining bleeding-free on day 21 of treatment
- To evaluate the number of treatment days before cessation of vaginal bleeding
- To evaluate the number of days of spotting/breakthrough bleeding during treatment
- To evaluate the number of days before recurrence of vaginal bleeding after stopping treatment
- To evaluate treatment side effects
- To evaluate treatment adherence

6. Research Question/Hypothesis

Do combined hormonal contraceptive patches containing Ethinyl Estradiol and Norelgestromin effectively treat irregular vaginal bleeding caused by contraceptive implant use compared to placebo?

7. Keywords

- Contraceptive implant
- Abnormal vaginal bleeding
- Bothersome vaginal bleeding
- Transdermal hormonal contraception
- Transdermal Ethinyl Estradiol and Norelgestromin
- Etonogestrel contraceptive implant
- Levonorgestrel contraceptive bleeding

8. Research Design

Randomized, double-blind, placebo-controlled trial

9. Research Methodology

Population: Contraceptive implant users with irregular vaginal bleeding after implant insertion

Participant Recruitment Approach: Recruit volunteers at the Family Planning Clinic, King Chulalongkorn Memorial Hospital, and advertise through posters

Inclusion Criteria:

1. Women aged 18 years and older
2. Regular menstrual cycles for at least 1 cycle before contraceptive implant insertion
3. Normal pelvic examination and transvaginal ultrasound results
4. Normal cervical cancer screening within 3 years
5. Irregular vaginal bleeding (bleeding for more than 8 consecutive days or bleeding-free intervals ≤15 days)

Exclusion Criteria:

1. Previous treatment for irregular vaginal bleeding within the past 3 months
2. Pregnancy

3. Contraindications to estrogen or progestin use
4. Allergy to estrogen or progestin
5. Allergy to hormonal patches
6. Heavy vaginal bleeding causing anemia symptoms (fatigue, fainting)

Informed Consent Process: Research assistants explain information to volunteers, distribute information sheets and consent forms at the Family Planning Clinic, King Chulalongkorn Memorial Hospital. Participants can take materials home for consideration before deciding to participate.

Research Methods:

1. Obtain ethics approval from the Research Ethics Committee, Faculty of Medicine, Chulalongkorn University
2. Recruit volunteers with informed consent from all participants
3. Collect baseline data including demographic data, pelvic examination, ultrasound
4. Randomization and treatment allocation using Block of 4 randomization via computer program with stratified randomization (etonogestrel contraceptive implant and levonogestrel contraceptive implant), prepared by personnel not involved in data analysis, with treatment providers blinded to study drug vs. placebo
    - **4.1 Study group:** Combined hormonal contraceptive patch containing Ethinyl Estradiol 600 micrograms and norelgestromin 6 milligrams for 21 days (1 patch per 7 days), manufactured by GEDEON RICHTER PLC. and imported by Abbott (manufacturers have no conflict of interest)
    - **4.2 Placebo group:** Patches identical in appearance to contraceptive patches without active ingredients (1 patch

per 7 days), manufactured and imported by Convatec (manufacturers have no conflict of interest)

5. Follow-up at 7 days, 14 days, 21 days, and 3 months. Day 14 will be onsite follow-up, while days 7, 21, and 3 months will be telephone follow-up
6. Create official Line account to remind volunteers to change patches and allow contact for problems such as patch detachment or side effect reporting
7. Management protocol for study and control groups reporting continued bothersome vaginal bleeding requiring additional treatment: On day 21 telephone follow-up, if still reporting bothersome daily vaginal bleeding, provide standard treatment with oral contraceptive containing Ethinyl Estradiol 300 micrograms and levonorgestrel 150 micrograms, 1 pack (21 tablets), 1 tablet daily
8. Data recording and evaluation using statistical analysis
9. Report research results in appropriate format
10. Summarize research results, discuss findings, and present to research committee

Sample Size Calculation: Based on studies examining combined hormonal contraceptive efficacy compared to placebo in treating irregular vaginal bleeding in contraceptive implant users, 87.5% in the combined hormonal contraceptive group and 37.5% in the placebo group reported bleeding cessation after treatment (9).

Using the formula for calculating sample size for difference between two proportions, with 80% power, 0.05 significance level, $Z(0.975) = 1.96$, and $Z(0.8) = 0.84$, the calculated sample size is 14 per group. With 30% dropout rate, the sample size is 20 per group, totaling 40 participants.

10. Data Collection

Collect data using case record forms and record in REDCap Database

11. Data Analysis and Statistics

Analyze data using SPSS Statistics with Intention-to-treat (ITT) analysis:

- **Baseline characteristics:** Descriptive statistics using percentage for categorical variables and mean ± standard deviation (SD) for normally distributed continuous variables, median (IQR) for non-normally distributed data
- **Between-group comparisons:** Chi-square test or Fisher's Exact test for categorical variables, Two independent sample t-test or Wilcoxon Mann-Whitney U test for continuous variables
- **Significance level:** 0.05

12. Ethical Considerations

Respect for Persons: Provide complete information until volunteers fully understand and freely decide to consent to participate. Data from studies and patient records will be kept confidential, considering patient rights as paramount. Data recording will not include patient-identifying information, and study results will present overall findings without individual data. Researchers must obtain patient consent before participation.

Beneficence/Non-maleficence: Patients will benefit from treatment and continuous follow-up. Adverse events can be reported directly to researchers. Patients may not benefit and may risk adverse effects from study drugs and placebo, such as patch allergies, hormone-related thrombosis, breast tenderness.

Justice: Clear inclusion and exclusion criteria, equal distribution of risks and benefits through randomization.

13. Expected Benefits

Understanding the efficacy of combined hormonal contraceptive patches containing Ethinyl estradiol and Norelgestromin in treating irregular vaginal bleeding in contraceptive implant users compared to placebo, to guide future clinical use.

14. Potential Challenges

Treatment compliance issues such as timely patch changes and premature patch detachment:

- Line official system for patient follow-up and patch change reminders
- 1 spare patch per volunteer for patch detachment cases

15. Risks and Investigator Responsibility

Drug side effects and adverse events:

- System for reporting side effects and drug complications. Serious side effects affecting participants will result in drug discontinuation and treatment.

16. Research Timeline

August 1, 2024 - July 31, 2026

17. Study Venue

Family Planning Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society

18. Research Management and Activity Schedule

- Research question formulation and literature review: Aug 1 - Sep 30, 2024
- Research proposal writing: Oct 1 - Oct 31, 2024

- Ethics committee approval and research funding: Feb 1 - Apr 30, 2025
- Research implementation after ethics approval: Aug 1, 2025 - Aug 1, 2026
- Data collection, statistical analysis, and report writing: Aug 1, 2026 - Sep 30, 2026
- Revision and research report preparation: Oct 1, 2026 - Nov 30, 2026

19. Post-Trial Access to Study Drug

Available through physician prescription