Cycle Control, Safety and Acceptability of a New Oral Contraceptive Containing Ethinylestradiol 15 Micrograms and Gestodene 60 Micrograms

Ladakan Jaithitivit MD*,
Unnop Jaisamrarn MD, MHS*, Surasak Taneepanichskul MD, MPH*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Objective: *To determine cycle control, safety, and acceptability of a 24-day oral contraceptive regimen containing 15 micrograms of ethinylestradiol and 60 micrograms of gestodene.*

Material and Method: *This was an open-label, non-comparative study. Healthy women 18 to 35 years old who attended the Family Planning Clinic of King Chulalongkorn Memorial Hospital were assigned to receive six cycles of the study oral contraceptives, administered daily for 24 days and followed by a 4-day hormone-free interval. Data on bleeding patterns, side effects, body weight, blood pressure, and satisfaction were collected. Descriptive statistics and paired t test were used for the analysis.*

Results: *Ninety-four women completed the present study. There was no pregnancy reported during the present study. Percentages of breakthrough bleeding and spotting were higher in the first cycle (2.1% and 6.4%), then decreased and disappeared after the third cycle. There was no significant change in the body weight and the blood pressure. Only minimal side effects were reported and 93.6% of the women were satisfied or very satisfied. Furthermore, 91.5% would continue using this oral contraceptive.*

Conclusion: *This new oral contraceptive, a combination of 15 micrograms of ethinylestradiol and 60 micrograms of gestodene has acceptable cycle control, minimal side effects, and good acceptability.*

Keywords: *Ethinylestradiol, Gestodene, Oral contraceptive, Cycle control*

J Med Assoc Thai 2012; 95 (5): 630-5
Full text. e-Journal: *http://www.jmat.mat.or.th*

Combined oral contraceptives (COCs) have been enormously popular and a highly effective contraceptive method[1]. In addition to their proven contraceptive efficacy, they are widely recognized as providing menstrual cycle-related benefits, including regular menstrual cycles, reducing menstrual flow and relief from dysmenorrhea. COCs have varied effectiveness and side effects, such as bleeding irregularities, nausea, vomiting, headaches and fluid-related symptoms (*e.g.* breast tenderness and bloating) depending on the types and combinations of estrogen and progestin[2]. Many women who were on contraception stopped taking oral contraceptives due to a number of reasons that include adverse effects, especially bleeding irregularities[2,3]. Bleeding irregularities can be found more in COCs containing low-dose estrogen when compared to higher dose[1].

The ongoing researches of COCs have been concentrated on reducing the dose of estrogen and progestrogen with the objective of maintaining contraceptive efficacy with the improvement of drug safety and acceptability. Among the newly developed progestogens, gestodene, desogestrel, and norgestimate exert a more selective progestational activity that improves cycle control and minimizes metabolic changes and adverse effects while effectively preventing pregnancy.

The ability of gestodene-containing oral contraceptives to inhibit ovulation is similar to that of preparations containing other progestogens although the required dosage is lower[4].

More recently, an ultra-low-dose contraceptive formulation containing gestodene (GTD) 60 micrograms (mcgs) and ethinylestradiol (EE) 15 micrograms (mcgs)

Correspondence to:
Jaisamrarn U, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Rama IV Rd, Bangkok 10330, Thailand.
Phone: 0-2256-4241
E-mail: dr.unnop@yahoo.com

administered daily for 24 days followed by a 4-day hormone-free interval was introduced with a view to offer the lowest available daily dose regimen while maintaining contraceptive efficacy and cycle control. A combination of GTD 60 mcgs and EE 15 mcgs results in 25% reduction in daily dose of the EE component and 20% reduction in GTD component compared to the COCs that contain EE 20 mcgs. A new extended regimen of 24/4 may decrease the hormone withdrawal symptoms and increase ovarian suppression[6-8].

Most studies of this new oral contraceptive were performed in Western women[2-4].

The bleeding patterns within the contraceptive methods were closely related to the geographical regions. Women who were using COCs in Europe had longer bleeding episodes and shorter bleeding-free intervals than women in Southeast Asia[5].

The aim of the present study was to determine the cycle control (bleeding pattern), safety and acceptability of a new ultra-low-dose, monophasic COCs containing EE 15 mcgs and GTD 60 mcgs in 24/4 regimen.

Material and Method

Study design

The present study was an open-label, non-comparative, and conducted at the Family Planning Clinic of King Chulalongkorn Memorial Hospital in accordance with the guidelines of the Good Clinical Practice. All participants gave their written informed consents according to protocol approved by the Institutional Review Board.

Study population

Ninety-four healthy women desirous for contraception at the Family Planning Clinic of King Chulalongkorn Memorial Hospital and had regular menstrual cycles were assigned the study medication. Healthy women who fulfilled with the inclusion criteria were recruited in the present study. The inclusion and exclusion criteria are listed in Table 1. The termination criteria were pregnancy during the present study and intolerated side-effect.

Study protocol and data collection

The subjects were assigned to receive a COC containing EE 15 mcgs and GTD 60 mcgs for 6 cycles without other backup contraceptive method. Each cycle consisted of a once-daily pill intake for 24 days, followed by four tablet-free days. The first tablet was taken on the first day of their menstruation, and one tablet per day thereafter.

Clinical assessment

Complete medical, obstetric, and gynecological histories were assessed to confirm the eligibility. Complete physical and gynecological examinations including vital signs, body weight, pelvic, cervical cytological smear, and breast examination were conducted during the pre-study screening; and, menstrual diary cards were given to each subject. The women were instructed on the method to collect the data of pill intake, dates of any missed pills, bleeding patterns (menstruation, breakthrough bleeding, or spotting), and side effects. They were seen on admission, after one, three, and six cycles of COCs. The data of histories, physical examination, vital signs, and body weight were recorded. Compliance was assessed by analyzing patients' records in diary cards regarding tablet intake along with the return of used, partially used or unused of packs. The cycle control was assessed by analyzing in the menstrual diary cards. Analysis of cycle control characteristics also included determinations of cycle length and the length of withdrawal bleeding episode, episode of breakthrough bleeding, spotting, and amenorrhea. Spotting was defined as very slight bleeding that required no sanitary protection, whereas breakthrough bleeding did require sanitary protection. A cycle was classified as 'normal' if the withdrawal bleeding started during the 7-day period after the last day of active pill intake, and the withdrawal bleeding did not extend beyond 11 days after the last active pill. Amenorrhea was defined as no bleeding during cycle. Episode of bleeding/spotting was defined as bleeding/spotting day bounded on either end by 2 days of no bleeding or spotting.

Table 1. Inclusion/exclusion criteria

Inclusion criteria
Healthy women age 18-35 years old
Preceding three regular menstrual cycles (21-35 days)
Request for at least six cycles of COCs
Did not previously use COCs or injectable contraceptives for 3 months
Willing to follow the trial procedure and undergo regular medical checkups
Exclusion criteria
Suspected of pregnancy or currently having pregnancy
Contraindication for COCs use according to the WHO categories 2, 3 and 4

Side effects were documented throughout the present study. The reasons of study withdrawal and dropouts were recorded. At the end of the present study (or premature withdrawal), the subjects were assessed for their acceptability with the study medication (based on the following categories: very satisfied; satisfied; neither satisfied nor dissatisfied; dissatisfied; and very dissatisfied). In addition, they were asked if they would continue the present study medication if it was made available.

Statistical analysis

An intent-to-treat analysis was conducted, which included all women who were randomly assigned to take at least one pill. Descriptive statistics were calculated, including the number of patients, mean, standard deviation for the subjects' demographics characteristics, bleeding patterns and side effects. Paired t-test was performed to analyze the significant difference in mean body weight and blood pressure.

As for the comparison between the means of the withdrawal bleeding length and cycle length between the first and the last cycle of the present study, repeated analysis of variance (ANOVA) was performed. The significance level was considered at 95% confidence interval. All statistical analyses were performed using SPSS version 17.0.

Results

Study population

Ninety-four women were recruited between October 2010 and June 2011. All subjects participated in the present study completely. There was no loss to follow-up or drop out. Subjects' baseline characteristics are shown in Table 2.

Table 2. Baseline characteristics of the subjects (n = 94)

Age (year)	27.6 ± 4.4
Height (cm)	157.3 ± 5.9
Weight (kg)	53.7 ± 6.2
BMI (kg/m^2)	21.4 ± 2.8
Blood pressure (mmHg)	
Systolic blood pressure	113.0 ± 6.9
Diastolic blood pressure	70.6 ± 6.4
Previous contraceptive method (%)	
Oral contraceptive	28.7
Condom	7.9
Intrauterine device	41.1
Other	1.1
None	21.2
Dysmenorrhea (%)	64.9

Continuous variables are presented as mean ± SD

Compliance

In the present study, 96.8% of the subjects reported taking the pills correctly. This showed good compliance throughout the present study.

Contraceptive efficacy

There was no occurrence of pregnancy during the present study.

Cycle control

The overall incidence of normal cycle was 86%. Fig. 1 and 2 shows the analysis of bleeding pattern of each cycle. The percentage of breakthrough bleeding was 2.1% in the first cycle and 4.3% in the second cycle. It then diminished until 0% through the sixth cycle. The percentage of spotting was 6.4%, 5.3%, and 4.4% in the first, second, and third cycle, respectively, then decreased until it disappeared after the third cycle. The incidence of amenorrhea was 1 to 3% during the first four cycles. No amenorrhea was found during the fifth and sixth cycle. The length

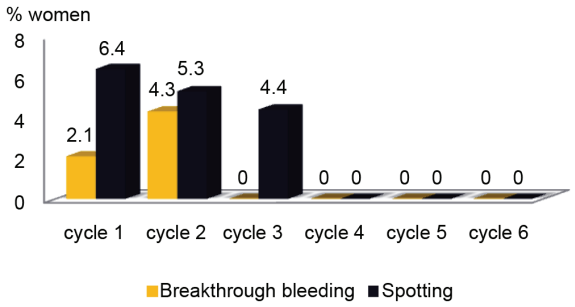

Fig. 1 Percentage of breakthrough bleeding and spotting in each cycle

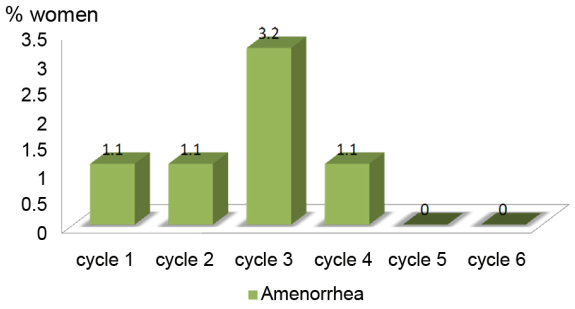

Fig. 2 Percentage of amenorrhea in each cycle

Table 3. Side effects (n = 17)

Side effects	%
Headache	11.7
Nausea and vomiting	3.2
Breast tenderness	2.1
Abdominal pain	1.1
Decrease libido	0
Emotional liability	0
Vaginal candidiasis	0
Acne	0
Dysmenorrhea	0

of withdrawal bleeding during use of this COC decreased from 4.5 days in the first cycle to 3.9 days in the sixth cycle. A statistically significant reduction in the length of withdrawal bleeding was observed after the sixth cycle as compared to the first cycle ($p = 0.000$).

Safety

Of the 94 women assessed, the most frequent side effect was headache, followed by nausea and vomiting, breast tenderness and abdominal pain. No dysmenorrhea was observed during the six cycles (Table 3). No change in body weight and blood pressure was observed during the present study.

Subject acceptability

Of those who responded in the full analysis set, 88 women (93.6%) were satisfied or very satisfied physically at the completion of the present study. In all, 90 women (95.8%) reported emotional satisfaction or high satisfaction. Only three (3.2%) and two (2.1%) women described physical and emotional dissatisfaction, respectively. In addition, 86 women (91.5%) would continue with the present study medication if they were given the choice.

Discussion

In the present study, the combination of GTD 60 mcgs/EE 15 mcgs administered daily for 24 days followed by a 4-day hormone-free interval, was proved to have acceptable cycle control, low side-effects, and high satisfaction rate.

Cycle control is extremely important, as it, along with the incidence of other side effects, is the strongest predictor, *i.e.*, whether a woman will use the pill correctly and continue with their use.

When compared to previous studies of the same COCs in Western women[7,8,10], the present study showed better cycle control. Moreover, the authors also found that this COCs combination provided better cycle control when compared to a previous study of higher dose COCs in Thai women[10]. A statistically significant reduction in the length of withdrawal bleeding was observed after the sixth cycle as compared to the first cycle ($p = 0.000$). However, there may be no significant difference in clinical. This positive development was expected with the use of ultra-low-dose contraceptives containing GTD. The cycle characteristics produced a bleeding pattern that was acceptable to subjects and no discontinuation due to irregular bleeding.

The side effects in the present study were typical for COCs, and similar to those reported in other studies such as headache, nausea, vomiting, and breast tenderness[6-9]. Dysmenorrhea decreased from 64% at baseline to 0% during study cycles. No subject discontinued the present study medication due to side effects. In the present study, there was no significant change from baseline regarding blood pressure and body weight.

The present study revealed a high rate of satisfaction of COC containing EE 15 mcgs and GTD 60 mcgs. In addition, the high satisfaction was reflected by the majority of the subjects reporting that they would continue the medication if it was available.

In conclusion, the findings of the present study show that this ultra-low-dose combination of EE 15 mcgs and GTD 60 mcgs has highly acceptable cycle control, good tolerability, low side effects and high satisfaction rate.

Acknowledgement

The authors wish to thank the staff and nurses of the Family Planning Clinic of King Chulalongkorn Memorial Hospital for their kind suggestions and assistance.

Potential conflicts of interest

None.

References

1. Schrager S. Abnormal uterine bleeding associated with hormonal contraception. Am Fam Physician 2002; 65: 2073-80.
2. Huber LR, Hogue CJ, Stein AD, Drews C, Zieman M, King J, et al. Contraceptive use and

discontinuation: findings from the contraceptive history, initiation, and choice study. Am J Obstet Gynecol 2006; 194: 1290-5.
3. Bachmann G, Korner P. Bleeding patterns associated with oral contraceptive use: a review of the literature. Contraception 2007; 76: 182-9.
4. Wilde MI, Balfour JA. Gestodene. A review of its pharmacology, efficacy and tolerability in combined contraceptive preparations. Drugs 1995; 50: 364-95.
5. Snowden R, Christian B. Patterns and perceptions of menstruation. J Biosoc Sci 2008; 16: 541-2.
6. Sullivan H, Furniss H, Spona J, Elstein M. Effect of 21-day and 24-day oral contraceptive regimens containing gestodene (60 microg) and ethinyl estradiol (15 microg) on ovarian activity. Fertil Steril 1999; 72: 115-20.
7. Cycle control, safety and efficacy of a 24-day regimen of gestodene 60 microg/ ethinylestradiol 15 microg and a 21-day regimen of desogestrel 150 microg/ethinylestradiol 20 microg. Eur J Contracept Reprod Health Care 1999; 4 (Suppl 2): 17-25.
8. Barbosa IC, Filho CI, Faggion D Jr, Baracat EC. Prospective, open-label, noncomparative study to assess cycle control, safety and acceptability of a new oral contraceptive containing gestodene 60 microg and ethinylestradiol 15 microg (Minesse). Contraception 2006; 73: 30-3.
9. Fruzzetti F, Genazzani AR, Ricci C, De Negri F, Bersi C, Carmassi F. A 12-month clinical investigation with a 24-day regimen containing 15 microg ethinylestradiol plus 60 microg gestodene with respect to hemostasis and cycle control. Contraception 2001; 63: 303-7.
10. Jaisamrarn U, Reinprayoon D, Virutamasen P. Clinical study of a monophasic pill containing 20 microg ethinylestradiol and 150 microg desogestrel in Thai women. J Med Assoc Thai 2001; 84 (Suppl 1): S377-83.
11. Sulak PJ, Kuehl TJ, Coffee A, Willis S. Prospective analysis of occurrence and management of breakthrough bleeding during an extended oral contraceptive regimen. Am J Obstet Gynecol 2006; 195: 935-41.
12. Steinauer J, Autry AM. Extended cycle combined hormonal contraception. Obstet Gynecol Clin North Am 2007; 34: 43-55.
13. World Health Organization, Department of Reproductive Health and Research. Medical eligibility criteria for contraceptive use [Internet]. 4th ed. Geneva: WHO; 2009 [cited 2010 Jan 15]. Available from: http://whqlibdoc.who.int/publications/2010/9789241563888_eng. pdf.
14. DelConte A, Loffer F, Grubb GS. Cycle control with oral contraceptives containing 20 micrograms of ethinyl estradiol. A multicenter, randomized comparison of levonorgestrel/ethinyl estradiol (100 micrograms/20 micrograms) and norethindrone/ethinyl estradiol (1000 micrograms/20 micrograms). Contraception 1999; 59: 187-93.
15. Belsey EM, Farley TM. The analysis of menstrual bleeding patterns: a review. Contraception 1988; 38: 129-56.
16. Belsey EM, Machin D, d'Arcangues C. The analysis of vaginal bleeding patterns induced by fertility regulating methods. World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction. Contraception 1986; 34: 253-60.
17. Cerel-Suhl SL, Yeager BF. Update on oral contraceptive pills. Am Fam Physician 1999; 60: 2073-84.
18. Creatsas G, Elsheikh A. Oral contraceptives-very low estrogen dosages: pros and cons [Internet]. 2010 [cited 2010 Jan 15]. Available from: www.comtecmed.com/COGI/COGI2_FullPapers/117.rtf

การควบคุมรอบระดู ผลข้างเคียงและการยอมรับของยาเม็ดคุมกำเนิดที่ประกอบด้วย ethinylestradiol 15 ไมโครกรัม และ gestodene 60 ไมโครกรัม

ลดากานต์ ใจฐิติวิทย์, อรรณพ ใจสำราญ, สุรศักดิ์ ฐานีพานิชสกุล

วัตถุประสงค์: เพื่อศึกษาการควบคุมรอบระดู ผลข้างเคียงและการยอมรับของยาเม็ดคุมกำเนิดที่ประกอบด้วย ethinylestradiol 15 ไมโครกรัมและ gestodene 60 ไมโครกรัม

วัสดุและวิธีการ: เป็นการศึกษาชนิดพรรณนา ในสตรีสุขภาพแข็งแรงอายุ 18-35 ปี ที่ต้องการคุมกำเนิด ณ คลินิกวางแผนครอบครัว โรงพยาบาลจุฬาลงกรณ์ โดยได้รับยาเม็ดคุมกำเนิดที่ประกอบด้วย ethinylestradiol 15 ไมโครกรัม และ gestodene 60 ไมโครกรัม รับประทานต่อเนื่องกัน 24 วัน และเว้น 4 วัน เป็นระยะเวลา 6 รอบ มีการเก็บข้อมูลเกี่ยวกับลักษณะรอบระดู ผลข้างเคียง การยอมรับ การเปลี่ยนแปลงน้ำหนักตัว และความดันโลหิต การวิเคราะห์ข้อมูลทางสถิติเชิงพรรณนาใช้ร้อยละ ค่าเฉลี่ยและส่วนเบี่ยงเบนมาตรฐาน และใช้ paired t test สำหรับเปรียบเทียบข้อมูลก่อนและหลังการศึกษา

ผลการศึกษา: สตรีเข้าร่วมการศึกษารวม 94 คน ไม่พบการตั้งครรภ์ในการศึกษานี้ มีอุบัติการณ์ของเลือดออกกะปริดกะปรอยแบบที่ต้องใช้และไม่ต้องใช้ผ้าอนามัยอยู่ในเกณฑ์ต่ำ เป็นร้อยละ 2.1 และ 6.4 ตามลำดับ โดยพบมากในรอบการศึกษาแรก และลดลงในรอบการศึกษาต่อมาจนไม่พบหลังรอบที่ 3 ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติของน้ำหนักตัวและความดันโลหิตก่อนและหลังการศึกษา พบผลข้างเคียงเล็กน้อย ไม่มีผู้ออกจากการศึกษาก่อนสิ้นสุดการศึกษา สตรีร้อยละ 93.6 รู้สึกพึงพอใจและพึงพอใจมาก และร้อยละ 91.5 มีความต้องการที่จะใช้ยาเม็ดคุมกำเนิดชนิดนี้ต่อไป

สรุป: ยาเม็ดคุมกำเนิดที่ประกอบด้วย ethinylestradiol 15 ไมโครกรัม และ gestodene 60 ไมโครกรัม สูตร 24/4 มีการควบคุมรอบระดูที่ยอมรับได้ อาการข้างเคียงน้อย และมีการยอมรับดี