A Study of Cycle Control, Side Effects and Client's Satisfaction of a Low Dose Combined Contraceptive Containing Ethinylestradiol/Drospirenone (24/4 Regimen)

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Objective: *To study cycle control, side effects, and satisfaction of low dose 24-day combined contraceptive containing 20 μg of Ethinylestradiol and 3 mg of Drospirenone.*

Material and Method: *This was an open label, non-comparative study. The healthy females from the family planning clinic at King Chulalongkorn Memorial Hospital were assigned to receive six cycles of combined oral contraceptive containing 20 μg of ethinylestradiol and 3 mg of drospirenone administered daily for 24 days followed by 4-day hormone-free interval. Data were collected on cycle control, side effects, and satisfaction. Data were analyzed using descriptive statistics for descriptive data and Paired t test for comparison.*

Results: *One hundred fifty four women were assigned the study medication, including one (0.64%) who did not start medication. In the second reference period, the occurrence of frequent and infrequent bleeding was low (2.1% and 4.9%). Only one woman (0.65%) discontinued medication because of irregular bleeding. There was no pregnancy reported during the present study. Overall, the study medication was well tolerated and five subjects (3.24%) discontinued study because of side effects. No serious side effects related to the study medication were reported. The majority of women (84.2%) were satisfied and very satisfied with the treatment and most (73.3%) would continue the medication if it were available.*

Conclusion: *The low dose combined contraceptive containing Ethinylestradiol/Drospirenone (24/4 regimen) has acceptable cycle control and good tolerability.*

Keywords: *Drospirenone, Ethinylestradiol, Combined oral contraceptives, Cycle control*

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Combined oral contraceptives (COCs) are popular and effective contraceptive methods[1], which has the proven contraceptive efficacy and many non-contraceptive benefits. The COCs have varied effectiveness, tolerability, and satisfaction depend on the different kind of estrogen and progestin. The ongoing research of COCs has focused on lowering the dose of estrogen to reduce the potential risk and side effects such as cardiovascular disease[2], venous thromboembolism, nausea, vomiting, and breast tenderness. The new progestins were also investigated to resemble the natural progesterone. Drospirenone is the new progestin, which has progestogenic, anti-mineralocorticoid, and antiandrogenic activities[3,4]. It also can counteract the water retention and symptoms such as breast tenderness and edema from estrogen induced renin-angiotensin system.

The lower estrogen doses cause an increased incidence of unscheduled bleeding and spotting (cycle control)[5,6], an important discontinuation factor of COCs[7-9]. The woman's perception of bleeding pattern is important and suggests the clinician to counsel about the possibility of bleeding problems, adverse effects, and tolerability issues (pelvic pain, headache, bloating, and breast tenderness). A new extended COCs containing 24 once daily hormone (20 μg of ethinylestradiol and 3 mg of drospirenone) followed by a four-day hormone free period may decrease the hormone withdrawal symptoms[10,11] and increase ovarian suppression[12].

The objectives of the present study were to study the cycle control, side effects and client's satisfaction of this low dose monophasic containing

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20 mcg of ethinylestradiol and 3 mg of drospirenone (24/4 regimen) in Thai women.

Material and Method

Study design

The present study was an open-label, non-comparative study and conducted at the family-planning clinic of the King Chulalongkorn Memorial Hospital in accordance with regulations governing good clinical practice. The protocol was approved by the ethics committee. All subjects gave written and informed consent prior to study participation.

Study population

One hundred fifty four healthy women desired contraception at the family planning clinic of King Chulalongkorn Memorial Hospital were assigned the study medication. Healthy women who fulfilled with the inclusion criteria were recruited in the present study. The inclusion criteria were age 18-35 years old, willing to follow the present study, request for at least six complete cycles of COCs, did not use COCs or injectable hormonal contraceptives within six months before the present study, and women must have had at least three regular menstrual cycles after removal of contraceptive implant or IUD, and after giving birth or abortion and before the present study. Exclusion criteria were suspected pregnancy or pregnancy, lactation, and any disorders that were contraindication following the WHO category 2, 3 and 4[13].

Study protocol and data collection

The participants were explained the risk and benefit and offered the chance to ask questions and to withdraw from the present study without giving the reasons. The participants signed the consent form after the data was informed. Each subject was assigned to receive a COC containing 20 μg of ethinylestradiol and 3 mg of drosperinone 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, taking one tablet per day thereafter.

Clinical assessments

The medical, obstetric, and gynecologic history was assessed to confirm the eligibility. The physical examination, including pelvic and breast examination, vital signs, body weight, and pelvic ultrasonography were collected before the COCs and menstrual diary cards was given. The participants were instructed about the methods to collect the data of pill intake, bleeding pattern, side effects, and satisfaction. They were seen on admission, and after three and six cycles of COCs. The data of histories, physical examination, vital signs, and weight were recorded and measured. Compliance was assessed by evaluating diary card of pills intake and the return of packs. The cycle control was assessed by analyzing episodes of intermenstrual bleeding and menstruation in the menstrual diary cards. The bleeding patterns were described using the 90-day reference period method recommended by the WHO[14,15]. Enrolled subjects were assigned to receive the study medication for six cycles (2 reference periods) and the first 90-day reference period started on the first day of the present study. Intermenstrual bleeding was summarized by duration and type. Amenorrhea was defined as no bleeding during the reference period. Infrequent bleeding was defined as fewer than three bleeding episodes per a reference period. Frequent bleeding was defined as more than five bleeding episodes per a reference period. Irregular bleeding defined as three and five episodes with less than three bleeding-free intervals of length 14 days or more per a reference period. Prolonged bleeding was defined as one or more bleeding episodes lasting 14 days or more per a reference period. Finally, none of the above was defined as normal bleeding pattern.

Side effects, both those observed by investigators and those reported by participants were documented throughout the present study. The reasons of study withdrawal and dropouts were documented. At the end of the present study or premature withdrawal, subjects were asked to give a subjective assessment of their satisfaction with the study medication. The levels of satisfaction were very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, and very dissatisfied. In addition, participants were asked if they would continue the study medication if it were available.

Statistical analysis

After the data for all participants were collected, all analyses were performed on the full analysis set (defined as all women who took at least one dose of the study medication and had at least one study observation). Descriptive statistics were calculated for the subjects' demographic characteristics, bleeding pattern and side effects. Paired t-test was conducted to analyze the significant difference in mean body

weight and blood pressure. The significance level was considered at 95% confidence interval. The statistical package SPSS version 13.0 was used to calculate all statistical analyses.

Results

One hundred fifty four women were recruited between August 2008 and June 2009, including one (0.64%) who did not start the medication. Of these, 153 women (99.3%) started treatment medication and had at least one study observation and formed the full analysis set. Twelve (7.8%) women discontinued the study prematurely for the reasons that included side effects (5 women [3.24%]), volunteered to conceive (1 woman [0.64%]), lost to follow-up (5 women [3.24%]), and unspecified reason (1 woman [0.64%]). Thus, 141 women (91.5%) completed the present study medication. Subjects' demographic and baseline characteristics are shown in Table 1. Sixty-one women (39.6%) had used a different COCs prior to study entry.

Compliance

The mean number of tablets taken in cycle 1 to 6 ranged between 27.8 $\pm$ 0.5 and 27.9 $\pm$ 0.3 tablets per cycle suggesting good compliance with the study medication. The proportion of women who took all 28 tablets in cycle 1 to 6 ranged 89.3% and 95.1%; 27 tablets ranged 4.2% and 10.1%; less than 27 tablets ranged 0.7% and 3.4%

Table 1. Baseline demographic characteristics at screening (n = 154)

Age (years)	26.8 $\pm$ 4.5
Height (cm)	156.8 $\pm$ 5.1
Weight (kg)	52.7 $\pm$ 7.8
BMI (kg/m^2)	21.4 $\pm$ 2.95
Mean blood pressure (mmHg)	
Systolic blood pressure	110.5 $\pm$ 8.9
Diastolic blood pressure	69.8 $\pm$ 5.9
Parity (%)	
0	45.5
1	40.3
$\geq$ 2	14.2
Contraceptive method before the study (%)	
Oral contraceptive	39.6
Condoms	9.7
Intrauterine device	0.6
Other	6.0
None	42.9

Continuous variables are presented as mean $\pm$ SD

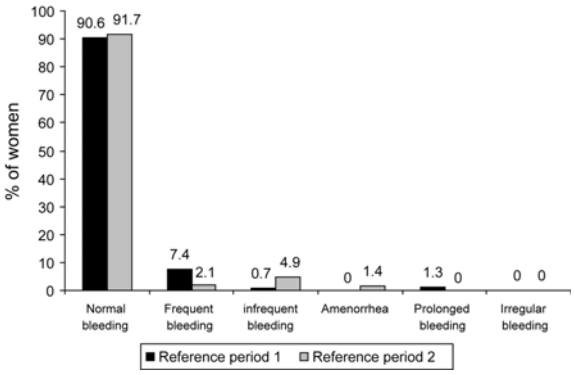

Fig. 1 Bleeding pattern during reference periods (A) 1 and (B) 2

Efficacy

There was no occurrence of pregnancy during the present study.

Bleeding pattern

The reference period analysis shows the pattern of bleeding profile (Fig. 1). The majority of women (91.7%) reported normal bleeding. The proportion of women reporting frequent bleeding was higher in the reference period 1 (7.4%). On the other hand, the proportion of women who reported infrequent bleeding increased from reference period 1 (0.7%) to reference period 2 (4.9%). Moreover, amenorrhea was experienced in two women (1.4%) during the present study. In addition, most of intermenstrual bleeding was restricted to spotting and only one case (0.65%) discontinued the medication because of bleeding problem. These findings suggested good acceptance of the study medication.

Table 2. Treatment related side effects (n = 45)

Side effect	No. of women (%)
Nausea and vomiting	8 (5.4%)
Breast pain	7 (4.8%)
Abnormal vaginal bleeding	7 (4.8%)
Headache	6 (4.1%)
Emotional lability	4 (2.7%)
Weight gain	4 (2.7%)
Abdominal pain, Bloating	3 (2.0%)
Dry skin, Cholasma	2 (1.4%)
Decreased libido	1 (0.7%)
Vaginal moniliasis	1 (0.7%)
Abdominal pain	1 (0.7%)
Acne	1 (0.7%)

Table 3. Effects on weight and blood pressure at the end of study

Characteristics	Baseline	After 6 cycles of treatment	Significance
Body weight (kg)[a]	53.00 ± 8.04	52.39 ± 7.79	0.0005
Systolic BP (mmHg)[a]	110.49 ± 9.01	110.07 ± 8.12	0.589
Diastolic BP (mmHg)[a]	69.86 ± 6.07	69.37 ± 6.65	0.444

[a] Values are mean ± SD

Side effects

The incidence of side effects was low, mild, transitory, and typically associated with COCs. Fourty-five (30.6%) women experienced at least one side effect, which is shown in Table 2. The frequent side effects were consistent with the other COCs treatment including nausea, vomiting, headache, breast tenderness, and irregular bleeding. Only five women (3.24%) discontinued the study medication prematurely due to side effects, which suggests good tolerability. No serious side effects were found.

There was no statistically significant difference from baseline in systolic and diastolic blood pressure. A slight decrease in body weight was observed during six cycles of treatment (Table 3). Finally, there was no evidence of any clinically changes from baseline in general physical and breast examination.

Subject Satisfaction

Of participants completing the present study, 84.2% of participants reported that they were satisfied or very satisfied at completion of the study. Only three participants (2.8%) stated dissatisfaction with treatment. In addition, 107 women (73.3%) would continue with this medication if it were available suggesting that this medication was generally well accepted.

Discussion

The result of the present study showed that the monophasic COCs containing ethinylestradiol 20 μg and drospirenone 3mg administered once daily for 24 days followed by a 4-day hormone-free interval provide acceptable cycle control, was well tolerated and was associated with a high proportion of clients' satisfaction. The intermenstrual bleeding was an important discontinuation factor. Therefore, the woman's perception of bleeding pattern before taken COCs is necessary. In the present study, only 0.65% of women discontinued prematurely the present study because of intracyclic bleeding and this incidence was similar when compared to other studies (0.7%-13%)[16-20]. The decrease of estrogen in new monophasic COC containing drospirenone still maintained acceptable cycle control when compared to other COC containing low dose estrogen[18,19].

The side effects in the present study were typical in COCs use and similar to other low dose COCs such as headache, nausea and vomiting and breast pain[21-23]. Five women (3.24%) discontinued the study medication due to side effects, which is similar to other COCs containing different progesterone and estrogen dose[16,21,24] suggesting that the present study of this COCs was well tolerated. Concern about weight gain can cause discontinuation of COCs and the available study is insufficient to determine the effects of this COCs formulation on body weight. In the present study, there was significant change in body weight between reference period 1 and period 2, which was consistent with the previous study that revealed 67% of enrolled subjects experienced weight reduction during the treatment[26]. In contrast, some previous studies showed that there was no clinically significant change in body weight[16,25]. The weight reduction may be explained by the association between antimineralcorticoid effect of drospirenone, decreased water retention, and total body fluid.

The present study revealed the high rate of satisfaction of COC containing drospirenone at the end of the study. More than 82% of subjects stated that they were satisfied and very satisfied. The result was also consistent with the other studies using 3 mg drospirenone and 20ug ethinylestradiol[16,17,24]. In addition, the high satisfaction was reflected by the majority of subjects reporting that they would continue with the medication if it were available.

In conclusion, the low dose combined contraceptive containing Ethinylestradiol and Drospirenone (24/4 regimen) had highly acceptable cycle control, good tolerability and high satisfaction rate.

References

1. Skouby SO. Contraceptive use and behavior in the 21st century: a comprehensive study across five European countries. Eur J Contracept Reprod Health Care 2004; 9: 57-68.
2. Chasan-Taber L, Stampfer MJ. Epidemiology of oral contraceptives and cardiovascular disease. Ann Intern Med 1998; 128: 467-77.
3. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception 2000; 62: 29-38.
4. Muhn P, Krattenmacher R, Beier S, Elger W, Schillinger E. Drospirenone: a novel progestogen with antimineralocorticoid and antiandrogenic activity. Pharmacological characterization in animal models. Contraception 1995; 51: 99-110.
5. Gallo MF, Nanda K, Grimes DA, Schulz KF. Twenty micrograms vs. >20 microg estrogen oral contraceptives for contraception: systematic review of randomized controlled trials. Contraception 2005; 71: 162-9.
6. Dionne P, Vickerson F. A double-blind comparison of two oral contraceptives containing 50 mu g. and 30 mu g. ethinyl estradiol. Curr Ther Res Clin Exp 1974; 16: 281-8.
7. Colli E, Tong D, Penhallegon R, Parazzini F. Reasons for contraceptive discontinuation in women 20-39 years old in New Zealand. Contraception 1999; 59: 227-31.
8. Rosenberg MJ, Waugh MS. Oral contraceptive discontinuation: a prospective evaluation of frequency and reasons. Am J Obstet Gynecol 1998; 179: 577-82.
9. Belsey EM. The association between vaginal bleeding patterns and reasons for discontinuation of contraceptive use. Contraception 1988; 38: 207-25.
10. Sulak PJ, Scow RD, Preece C, Riggs MW, Kuehl TJ. Hormone withdrawal symptoms in oral contraceptive users. Obstet Gynecol 2000; 95: 261-6.
11. Sulak PJ, Kuehl TJ, Ortiz M, Shull BL. Acceptance of altering the standard 21-day/7-day oral contraceptive regimen to delay menses and reduce hormone withdrawal symptoms. Am J Obstet Gynecol 2002; 186: 1142-9.
12. Spona J, Elstein M, Feichtinger W, Sullivan H, Ludicke F, Muller U, et al. Shorter pill-free interval in combined oral contraceptives decreases follicular development. Contraception 1996; 54: 71-7.
13. World Health Organization, Department of Reproductive Health and Research. Medical eligibility criteria for contraceptive use [database on the Internet]. 3rd ed. Geneva: WHO; 2004 [cited 2009 Jul 20]. Available from: http://whqlibdoc.who.int/publications/2004/9241562668.pdf
14. 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.
15. Belsey EM, Farley TM. The analysis of menstrual bleeding patterns: a review. Contraception 1988; 38: 129-56.
16. Bachmann G, Sulak PJ, Sampson-Landers C, Benda N, Marr J. Efficacy and safety of a low-dose 24-day combined oral contraceptive containing 20 micrograms ethinylestradiol and 3 mg drospirenone. Contraception 2004; 70: 191-8.
17. Cibula D, Karck U, Weidenhammer HG, Kunz J, Alincic S, Marr J. Efficacy and safety of a low-dose 21-day combined oral contraceptive containing ethinylestradiol 20microg and drospirenone 3 mg. Clin Drug Investig 2006; 26: 143-50.
18. Akerlund M, Rode A, Westergaard J. Comparative profiles of reliability, cycle control and side effects of two oral contraceptive formulations containing 150 micrograms desogestrel and either 30 micrograms or 20 micrograms ethinyl oestradiol. Br J Obstet Gynaecol 1993; 100: 832-8.
19. Anderson FD, Hait H. A multicenter, randomized study of an extended cycle oral contraceptive. Contraception 2003; 68: 89-96.
20. Bounds W, Vessey M, Wiggins P. A randomized double-blind trial of two low dose combined oral contraceptives. Br J Obstet Gynaecol 1979; 86: 325-9.
21. Endrikat J, Dusterberg B, Ruebig A, Gerlinger C, Strowitzki T. Comparison of efficacy, cycle control, and tolerability of two low-dose oral contraceptives in a multicenter clinical study. Contraception 1999; 60: 269-74.
22. Archer DF, Maheux R, DelConte A, O'Brien FB. A new low-dose monophasic combination oral contraceptive (Alesse) with levonorgestrel 100 micrograms and ethinyl estradiol 20 micrograms. North American Levonorgestrel Study Group (NALSG). Contraception 1997; 55: 139-44.
23. Boerrigter PJ, Ellman H, Dolker M. International clinical experience with a new low-dose, monophasic oral contraceptive containing levonorgestrel 100

microg and ethinyl estradiol 20 microg. Clin Ther 1999; 21: 118-27.
24. Hernadi L, Marr J, Trummer D, De Loe V, Petraglia F. Efficacy and safety of a low-dose combined oral contraceptive containing drospirenone 3 mg and ethinylestradiol 20 mcg in a 24/4-day regimen. Contraception 2009; 80: 18-24.
25. Endrikat JS, Milchev NP, Kapamadzija A, Georgievska J, Gerlinger C, Schmidt W, et al. Bleeding pattern, tolerance and patient satisfaction with a drospirenone-containing oral contraceptive evaluated in 3488 women in Europe, the Middle East and Canada. Contraception 2009; 79: 428-32.
26. Short M. User satisfaction with the combined oral contraceptive drospirenone 3 mg/ethinylestradiol 20 microg (Yasminelle) in clinical practice: a multi-country, questionnaire-based study. Clin Drug Investig 2009; 29: 153-9.

การศึกษาลักษณะประจำเดือน ผลข้างเคียงและความพึงพอใจของยาคุมกำเนิดที่ประกอบด้วย Ethinylestradiol และ Drospirenone สูตร 24/4

นพดล ไชยสิทธิ์, สุรศักดิ์ ฐานีพานิชสกุล

วัตถุประสงค์*: เพื่อศึกษาลักษณะประจำเดือน ผลข้างเคียง และความพึงพอใจของยาคุมกำเนิดชนิดรับประทานที่ประกอบด้วย Ethinylestradiol 20 ไมโครกรัมและ Drospirenone 3 มิลลิกรัม สูตร 24/4*

วัสดุและวิธีการ*: เป็นการศึกษาชนิดพรรณา ทำการศึกษาในหญิงสุขภาพดีที่ต้องการการคุมกำเนิด ในคลินิควางแผนครอบครัวโรงพยาบาลจุฬาลงกรณ์ โดยได้รับประทานยาคุมกำเนิดที่ประกอบด้วยethinylestradiol 20 ไมโครกรัม และ drospirenone 3 มิลลิกรัม รับประทานต่อเนื่องกันวันละ 1 เม็ด เป็นเวลา 24 วันและเว้น 4 วัน เป็นระยะเวลา 6 รอบ โดยรวบรวมข้อมูลเกี่ยวกับลักษณะรอบประจำเดือน ผลข้างเคียงและความพึงพอใจ การวิเคราะห์ข้อมูลทางสถิติเชิงพรรณาใช้ร้อยละ ค่าเฉลี่ยและส่วนเบี่ยงเบนมาตรฐานและใช้ Paired t test สำหรับเปรียบเทียบข้อมูลก่อนและหลังการศึกษา*

ผลการศึกษา*: ผู้เข้าร่วมการศึกษาและวิจัยรวม 154 คน อุบัติการณ์เลือดออกกะปริดกะปรอยอยู่ในเกณฑ์ต่ำ โดยมีรูปแบบเป็นระดูมาห่างและระดูมาถี่เป็นร้อยละ 2.1 และ 4.9 ตามลำดับ มีผู้ออกจากการศึกษาก่อนจบการศึกษาเนื่องจากปัญหาเลือดออกกะปริดกะปรอย 1 คน คิดเป็นร้อยละ 0.65 ไม่พบการตั้งครรภ์ในการศึกษานี้ มีผู้ออกจากการศึกษาก่อนจบการศึกษาเนื่องจากผลข้างเคียงจากยา 5 คน คิดเป็นร้อยละ 3.24 ผลข้างเคียงที่พบบ่อย ได้แก่ คลื่นไส้อาเจียน เต้านมคัดตึง ปวดศีรษะและเลือดออกกะปริดกะปรอย ไม่พบผลข้างเคียงรุนแรง ร้อยละ 84.2 พึงพอใจและพึงพอใจมากกับยาคุมชนิดนี้ และร้อยละ 73.3 ถ้ามีโอกาสจะใช้ยาคุมกำเนิดชนิดนี้ต่อ*

สรุป*: ยาคุมกำเนิดชนิดรับประทานที่ประกอบด้วย Ethinylestradiol 20 ไมโครกรัมและ Drospirenone 3 มิลลิกรัม สูตร 24/4 ลักษณะรอบประจำเดือนและผลข้างเคียงอยู่ในเกณฑ์ยอมรับได้*