A Randomized Controlled Trial of Clinical Usage between Desogestrel and Lynestrenol for Oral Contraception in Postpartum Women

Manopchai Thamkhantho MD, FRCOG, FRTCOG, MSc*, Nuchamon Wetphitthayakhom MD, FRTCOG*

* Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objective: *To evaluate vaginal bleeding patterns, side-effects, and acceptability between desogestrel and lynestrenol as a post-partum oral contraception.*

Material and Method: *The prospective open-labelled, randomized controlled trial was conducted in postpartum women at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. The inclusion criteria were 6-month breast feeding women, previous regular menses, body mass index (BMI) of less than 28.5 kg/m^2 and no contra-indications for progestogen only pills usage. Each woman was randomly assigned to either lynestrenol 500 mcg/day or desogestrel 75 mcg/day. Vaginal bleeding patterns, side-effects, and acceptability were compared at 3- and 6-month.*

Results: *Forty-five women were enrolled. Unscheduled bleeding was not different between the groups at 3- and 6-month. The other side effects e.g., acne, breast engorgement, headache, and nausea were not different between the groups at 3- and 6-month. The acceptability was higher in desogestrel group than lynestrenol group at 6-month (43.5% vs. 22.7%, p = 0.004).*

Conclusion: *Unscheduled bleeding and side effects were not different. However, acceptability at 6-month was higher in desogestrel group. Both drugs can be safely used as postpartum oral contraception.*

Keywords: *Desogestrel, Lynestrenol, Vaginal bleeding, Side effects, Acceptability, Postpartum oral contraception*

J Med Assoc Thai 2017; 100 (12): 1249-54
Website: http://www.jmatonline.com

Combined oral contraceptive pills[1] have been used worldwide. However, combined pills can cause some undesirable side effects such as breast tenderness, headache, nausea, and vomiting, and cannot be used by every woman. History of thrombo-embolism, liver diseases, current smoking, suspected or having breast cancer, or during lactation are the contra-indications. Hence, estrogen-free or progestin hormonal contraceptive pills is an alternative option in these women.

One estrogen-free contraceptive pill, a 500 mcg-lynestrenol oral contraceptive pill is commercially available. However, this progestin contraceptive pill is not commonly used due to some disadvantages, particularly irregular vaginal bleeding and amenorrhea[2,3]. In addition, its main contraceptive mechanisms are to thicken cervical mucus, poor endometrial condition for fetal implantation, and inhibition of ovulation. Unfortunately, the last mechanism is only 50% effective leading to inefficient contraception. Menstrual bleeding is also unpredictable[4,5]. In order to increase its efficacy, a recommendation is to take the pill at the same time very day[6].

Another estrogen-free contraceptive pill, a 75 mcg-desogestrel is recently available. Its contraceptive efficacy is much higher than traditional progestin-free oral contraceptive pill and is comparable to combined oral contraceptive pills with 99% rate of ovulation inhibition[4,7,8]. Moreover, its benefit over estrogen-containing pills is lacking of estrogen side effects and the administration can be delayed within 12 hours without lowering its efficacy[9]. However, irregular vaginal bleeding is still the major side effect and usage limitation[10,11]. The unpredictable menstrual bleeding may present in many different patterns. Some women may experience continuous bleeding for a few days followed by slight spotting for almost the entire month at the initial application of the pills. Other women may have a few bleeding days for many episodes and some may experience no bleeding days at all either after initiation of the drug or after a few cycles[6,12].

The objectives of the present study were to compare the effects of 500 mcg-lynestrenol and

Correspondence to:

Thamkhantho M. Unit of Gynecologic ID and Female STD, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: +66-81-9323378, Fax: +66-2-4194997
E-mail: tmanopchai@hotmail.com

75 mcg-desogestrel in term of the patterns of vaginal bleeding, side effects, and acceptability among post-partum breastfeeding women during the 6-month period.

Material and Method

Subjects

After the Siriraj Institutional Research Board approval and written informed consent obtained, a prospective, open-labelled, randomized controlled trial was conducted during their routine postpartum visit at the Family Planning Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University between November 2010 and October 2011. The inclusion criteria were women aged between 19 and 45 years, had history of regular menstruation before their recent pregnancy, desired to have contraception for at least six months, planned for 6-month breast feeding, had a body mass index (BMI) of less than 28.5 kg/m^2, and no contraindications for hormonal usage[2]. Pap smear test was performed in all women. The exclusion criteria were vaginal bleeding of unknown cause, previous history of ectopic pregnancy, currently pregnant, hypertension, or current concomitant drug use e.g., rifampicin, antibiotics, antiretroviral, antifungals, anticonvulsants, and sedatives. Any women who became pregnant during the course of the study was withdrawn from the study and recorded.

The advantages, disadvantages, duration of drug use, and schedule for follow-up visits were explained to all women. Participants were divided into two groups, A and B, by Blocked computerize randomization. Group A was provided with the 75 mcg-desogestrel and Group B with 500 mcg-lynestrenol. Each woman was followed-up at 3- and 6-month. Every women were required to record any bleeding/spotting (Table 1)[13]. The side effects and acceptability were recorded as well as the physical examination, body weight, and blood pressure.

Sample size calculation based on the percentage of unscheduled bleeding. Unscheduled bleeding was 50% in the lynestrenol group from a previous study[18]. We assumed that unscheduled bleeding was 10% in the desogestrel group. Seventeen cases were required for each group. Twenty percent was added for withdrawal. Thus, at least 21 cases were required for each group.

Statistical Package for the Social Science program (SPSS) for Window version 17 was used for the data analysis. Frequency, percentage, and mean were used for descriptive statistics. Chi-square test, McNemar's test, and the Fisher's exact test were used for the comparison of bleeding, side effects, and acceptability between groups. A *p*-value of less than 0.05 was considered as statistically significant.

Approval of the Siriraj Institutional Research Board (SiIRB)

The present research project had been approved by the IRB of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand on October 5, 2010, IRB No. Si523/2010.

Results

Forty-five post-partum breastfeeding women were enrolled, twenty-two and twenty-three women were allocated into group A and B, respectively. The demographic data is shown in Table 2. There were no statistically significant difference of characteristics of women between groups in terms of their age, BMI, and blood pressure.

Vaginal bleeding pattern is shown in Table 3. There was no statistically significant difference in unscheduled bleeding between the two groups. However, when vaginal bleeding pattern had been regrouped as "acceptable" (infrequent and amenorrhea) and "unacceptable" (prolonged and frequent), the desogestrel group had more acceptable bleeding pattern than the lynestrenol group without statistical significance at 3-month (*p*-value = 0.375) and with statistical significance at 6-month (*p*-value = 0.004).

Considering the other side effects such as acne, breast engorgement, headache, and nausea, the

Table 1. Classification of bleeding per vagina (modified from WHO 90-day reference period of bleeding vagina[14])

Bleeding per vagina*	
Infrequent	Bleeding less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)
Amenorrhea	No bleeding and/or spotting in 90 days
Prolonged	More than seven bleeding days in 90 days
Frequent	More than five bleeding and/or spotting episodes in 90 days

* The definition of bleeding per vagina are: 1) any bloody vaginal discharge that requires the use of such protection as pads or tampons, 2) loss of blood required 2 sanitary pads or tampons per day

side effects were not different between the groups at 3- and 6-month (Table 4). No serious adverse events or incidental pregnancy were encountered in both groups during the course of the present study.

The acceptability of women during the study drugs use were compared at 3- and 6- month (Table 4). Desogestrel group had more acceptability than lynestrenol group at 6-month (43.5% vs. 22.7%, $p = 0.004$).

Discussion

The present study was a prospective open-labelled, randomized controlled trial comparing desogestrel with lynestrenol. It demonstrated that unscheduled bleeding and side effects are not different. However, the acceptability at 6-month was higher in the desogestrel group than in the lynestrenol group.

The most reported vaginal bleeding pattern was the frequent bleeding, which was commonly found in the third month and decreased within six months. Prolonged bleeding was minimally reported in both groups for the entire study.

Both drugs had provided the women with highly effective protection against pregnancy and minimal side effects. Vaginal bleeding patterns induced by these two study drugs were not different. It can be concluded that both of these progestogen-only oral contraceptive pills can safely be used with high contraceptive efficacy among postpartum women as there was no accidental pregnancy over the course of the present study. The side effects were also minimally reported. The most found bleeding pattern was the frequent bleeding, which was found in the first three months of use. However, there was a likelihood of diminishing over times of use, in particular among women taking desogestrel. Amenorrhea or infrequent bleeding was also more likely to happen when used beyond six months[14,15]. Proper and close counseling during the course of use on the irregularity of bleeding is highly recommended when using progestogen only oral contraceptive pills to reach the most effective use of this kind of contraceptive method, and the continuation of use. Both drugs would be a good alternative method or an option for postpartum women who are breastfeeding and want to use oral contraceptive pills as a method of pregnancy prevention. However, the present study did not assess the volume of milk during the course of breastfeeding and contraceptive use. It hence cannot indicate if these two study drugs of oral contraceptive pills affect the volume of milk during breastfeeding. At each follow-up visit, breast

Table 2. Demographic data (n = 45)

Categories	Desogestrel (n = 22) mean ± SD	Lynestrenol (n = 23) mean ± SD	*p*-value
Age (year)	26.9±4.4	26.6±5.0	0.83
BMI (kg/m^2)	22.8±2.7	23.0±3.6	0.82
SBP (mmHg)	104.0±11.0	103.0±10.8	0.71
DBP (mmHg)	67.8±7.2	66.7±5.6	0.68

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure

Table 3. Comparison of vaginal bleeding pattern at 3- and 6-month period

Bleeding pattern	3-month period			6-month period		
	Desogestrel (n = 22)	Lynestrenol (n = 23)	*p*-value*	Desogestrel (n = 22)	Lynestrenol (n = 23)	*p*-value*
Infrequent	1 (4.6)	2 (8.7)	1.00	2 (9.1)	2 (8.7)	0.438
Amenorrhea	7 (31.8)	8 (34.8)		15 (68.2)	11 (47.8)	
Prolonged	0 (0.0)	0 (0.0)		0 (0.0)	1 (4.4)	
Frequent	14 (63.6)	13 (56.5)		5 (22.7)	9 (39.1)	
Total	22 (100)	23 (100)		22 (100)	23 (100)	

Data presented as n (%), * Fisher's exact test

Table 4. Comparison of the other side effects and acceptability at 3- and 6-month period

Side effects	3-month period			6-month period		
	Desogestrel, n (%)	Lynestrenol, n (%)	*p*-value	Desogestrel, n (%)	Lynestrenol, n (%)	*p*-value
Acne	6 (27.3)	6 (25.0)	1.00	4 (18.2)	0 (0.0)	0.05
Breast engorgement	8 (36.4)	17 (29.2)	0.84	3 (13.6)	1 (4.3)	0.35
Headache	8 (36.4)	6 (25.0)	0.60	1 (4.5)	3 (13.0)	0.60
Nausea	2 (22.7)	3 (12.5)	0.45	0 (0.0)	0 (0.0)	0.00
Acceptability	8 (36.4)	10 (43.5)	0.375	17 (77.3)	13 (56.5)	0.004

feeding status of each woman was checked and recorded. No problem was found[16,17].

Other side effects such as breast engorgement, headache, and nausea occurred at the beginning of the drug initiation but eventually subsided along the course of use. There was no change in the body weight and blood pressure among these breastfeeding women at the third month and sixth month follow-up visits. The acceptability was higher in desogestrel group than lynestrenol group at 6-month.

Conclusion

Unscheduled bleeding and side effects were not different between these two study drugs. However, the acceptability at 6-month was higher in the desogestrel group. Both study drugs can be safely used as postpartum contraception with high contraceptive efficacy. Both progestogen-only oral contraceptives caused less troublesome abnormal vaginal bleeding over the course of use, although frequent bleeding was predominant at the beginning of the use. The strength of the present research is that it was a randomized clinical study comparing the study drugs between desogestrel and lynestrenol regarding the unscheduled bleeding during study period. Knowledge from the present study can be applied in the family planning services while advising postpartum breastfeeding women as a choice of contraceptive use. Besides, the limitation of the present study is its small sample size, which can impact the strength of the study. The authors would recommend a similar trial should contain a larger sample size to clearly reach the solid outcome. However, this is the first comparative study between these two study drugs ever carried out in Thailand.

What is already known on this topic?

Oral contraceptive pill has widely been used, especially the combined contraceptive pills. However, the progestogen only contraceptive pill has not yet played a vital role in acceptance of the method due to side effects of progestogen hormone[2] itself such as irregularity of bleeding, amenorrhea and breast engorgement, headache, and nausea. Progestogen only pills have an advantage in terms of breastfeeding because it does not affect the quantity and quality of the breast milk[5]. Discontinuation of the progestogen only pills mostly occurs due to the unscheduled vaginal bleeding[8]. This has led to discontinue the use of family planning method, which may result in unwanted pregnancy. The new progestogen only pill, desogestrel 75 mcg, has been developed over a decade to improve the contraceptive efficacy. Its mechanism makes the cervical mucus thicken, thus, inhibits the ovulation.

What this study adds?

Unscheduled bleeding and side effects were not different between desogestrel 75 mcg and lynestrenol 500 mcg, but acceptability in terms of infrequent bleeding and amenorrhea at 6-month was higher in the desogestrel 75 mcg group. In this regard, it is suggested that development of doses and types of progestogens are still required to reach a better progestogen only pill to suit the women and their contraceptive goal in the future. The progestogen only pill should play a more important role as a contraceptive method for extensive use, not limited to the breastfeeding mothers but among women with estrogen-induced side effects such as severe migraine and venous thromboembolism.

Acknowledgement

The authors would like to thank all contributing members of the Faculty of Medicine Siriraj Hospital for their works, particularly the Siriraj Family Planning Clinic members. Last but not least, the authors would like to sincerely thank Associate Professor Surasak Angsuwatana, Head of Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University for his great support of the work.

Potential conflicts of interest

None.

References

1. Liang SY, Babcock HM. Commentary. Update on emerging infections: news from the Centers for Disease Control and Prevention. Ann Emerg Med 2012; 60: 628-31.
2. Hall KS, Trussell J, Schwarz EB. Progestin-only contraceptive pill use among women in the United States. Contraception 2012; 86: 653-8.
3. Liang SY, Grossman D, Phillips KA. User characteristics and out-of-pocket expenditures for progestin-only versus combined oral contraceptives. Contraception 2012; 86: 666-72.
4. Grimes DA, Lopez LM, O'Brien PA, Raymond EG. Progestin-only pills for contraception. Cochrane Database Syst Rev 2010; CD007541.
5. Chi I. The safety and efficacy issues of progestin-only oral contraceptives--an epidemiologic perspective. Contraception 1993; 47: 1-21.
6. Schrager S. Abnormal uterine bleeding associated

with hormonal contraception. Am Fam Physician 2002; 65: 2073-80.
7. Rice CF, Killick SR, Dieben T, Coelingh BH. A comparison of the inhibition of ovulation achieved by desogestrel 75 micrograms and levonorgestrel 30 micrograms daily. Hum Reprod 1999; 14: 982-5.
8. de Melo NR. Estrogen-free oral hormonal contraception: benefits of the progestin-only pill. Womens Health (Lond) 2010; 6: 721-35.
9. Korver T, Klipping C, Heger-Mahn D, Duijkers I, van Osta G, Dieben T. Maintenance of ovulation inhibition with the 75-microg desogestrel-only contraceptive pill (Cerazette) after scheduled 12-h delays in tablet intake. Contraception 2005; 71: 8-13.
10. Dunson TR, McLaurin VL, Aguayo EL, de Silva P, Calventi V, Gerais AS, et al. A multicenter comparative trial of triphasic and monophasic, low-dose combined oral contraceptives. Contraception 1993; 47: 515-25.
11. Espey E, Ogburn T, Leeman L, Singh R, Ostrom K, Schrader R. Effect of progestin compared with combined oral contraceptive pills on lactation: a randomized controlled trial. Obstet Gynecol 2012; 119: 5-13.
12. Bachmann G, Korner P. Bleeding patterns associated with oral contraceptive use: a review of the literature. Contraception 2007; 76: 182-9.
13. 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.
14. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. Eur J Contracept Reprod Health Care 1998; 3: 169-78.
15. Ferguson H, Vree ML, Wilpshaar J, Eskes TK. Multicenter study of the efficacy, cycle control and tolerability of a phasic desogestrel-containing oral contraceptive. Eur J Contracept Reprod Health Care 2000; 5: 35-45.
16. Tankeyoon M, Dusitsin N, Chalapati S, Koetsawang S, Saibiang S, Sas M, et al. Effects of hormonal contraceptives on milk volume and infant growth. WHO Special Programme of Research, Development and Research Training in Human Reproduction Task force on oral contraceptives. Contraception 1984; 30: 505-22.
17. Sinchai W, Sethavanich S, Asavapiriyanont S, Sittipiyasakul V, Sirikanchanakul R, Udomkiatsakul P, et al. Effects of a progestogen-only pill (Exluton) and an intrauterine device (Multiload Cu250) on breastfeeding. Adv Contracept 1995; 11: 143-55.
18. Diaz S, Zepeda A, Maturana X, Reyes MV, Miranda P, Casado ME, et al. Fertility regulation in nursing women. IX. Contraceptive performance, duration of lactation, infant growth, and bleeding patterns during use of progesterone vaginal rings, progestin-only pills, Norplant implants, and Copper T 380-A intrauterine devices. Contraception 1997; 56: 223-32.

การศึกษาเปรียบเทียบภาวะเลือดออกทางช่องคลอด ผลข้างเคียง และการยอมรับระหว่างยา desogestrel และ lynestrenol ซึ่งใช้เป็นยาคุมกำเนิดชนิดรับประทานแบบฮอร์โมนเดี่ยวหลังคลอด

มานพชัย ธรรมคันโธ, ณัฐชามญฑ์ เวทย์พิทยาคม

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบภาวะเลือดออกทางช่องคลอด ผลข้างเคียง และการยอมรับระหว่างยา desogestrel และ lynestrenol ซึ่งใช้เป็นยาคุมกำเนิดชนิดรับประทานแบบฮอร์โมนเดี่ยวหลังคลอด*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาทดลองแบบเปิดและสุ่มไปข้างหน้าระหว่างยา desogestrel และ lynestrenol ซึ่งทำการศึกษา ณ หน่วยวางแผนครอบครัว โรงพยาบาลศิริราช โดยมีเกณฑ์การคัดเลือกตามที่ได้รับอนุมัติจากคณะกรรมการวิจัยในคนสตรีผู้เข้าร่วมการศึกษาทั้งสิ้น 45 คน แบ่งเป็นกลุ่มละประมาณ 23 คน แบบสุ่ม มีการเก็บข้อมูลเพื่อนำไปวิเคราะห์ ภาวะเลือดออกทางช่องคลอด ผลข้างเคียง และการยอมรับ ณ ช่วงเวลา 3 และ 6 เดือน ตามลำดับ*

ผลการศึกษา: *ภาวะเลือดออกผิดปกติทางช่องคลอดไม่แตกต่างกันระหว่าง 2 กลุ่ม ณ ช่วงเวลา 3 และ 6 เดือน ส่วนผลข้างเคียงอื่นๆ เช่น สิว เต้านมตึง ปวดหัว และคลื่นไส้ไม่พบความแตกต่างระหว่างยาที่ทำการศึกษาทั้ง 2 ชนิด เช่นกัน แต่การยอมรับในยาคุมกำเนิดชนิดรับประทานหลังคลอด desogestrel สูงกว่า lynestrenol ณ 6 เดือน หลังทำการศึกษาอย่างมีนัยสำคัญทางสถิติ (43.5% และ 22.7%, p = 0.004)*

สรุป: *Desogestrel และ lynestrenol ไม่มีความแตกต่างด้านภาวะเลือดออกผิดปกติทางช่องคลอดหรือผลข้างเคียงอื่นๆ ในช่วงเวลา 3 และ 6 เดือน ที่ทำการศึกษา แต่การยอมรับในยาคุมกำเนิดชนิดรับประทานหลังคลอด desogestrel สูงกว่า lynestrenol ณ 6 เดือน หลังทำการศึกษา*