A Randomized Trial on the Impact of Starting Day on Ovarian Follicular Activity in Very Low Dose Oral Contraceptive Pills Users

SOMKIAT SITAVARIN, MD*,
UNNOP JAISAMRARN, MD, MHS*,
SURASAK TANEEPANICHSKUL, MD, MPH*

Abstract

In a randomized trial, the impact of starting day (the first and the seventh day of the period) on ovarian follicular activity was assessed during administration of a very low dose of oral contraceptive pills (20 microgram (mcg) ethinyl estradiol (EE) and 75 mcg gestodene (GS) [Meliane, Schering, Germany]). One hundred and sixty healthy women aged: 23-44 years, who had a regular cycle, and who were not using any type of oral contraceptive (OCs) steroid were studied at the Family Planning Clinic of King Chulalongkorn Memorial Hospital, Bangkok, Thailand. In the trial, each subject received a package of Meliane. They were blockwise randomized, 1 : 1 ratio; in the first group, subjects began their pills on the first day of their period (n = 80) and the other group, the seventh day of their period (n = 80). During the treatment cycle, ovarian activity was evaluated by transvaginal sonography (TVS) to determine the follicular-like structure (FLS). Ovulation was defined as the dominant FLS detected by TVS and followed-up every other day until its collapse. It occurred in 0 of 77 cases who started on the first day of their period and occurred in 8 of 78 cases of the group which started on the seventh day of their period. The difference was of statistical significance (p = 0.006). The result of this clinical trial is beneficial information for users of OCs containing 20 mcg EE who delay start of the OCs package.

Key word : Oral Contraceptive, Follicular Liked Structure, Ovulation

SITAVARIN S, JAISAMRARN U, TANEEPANICHSKUL S
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It is estimated that 78 million people worldwide are using oral contraception[1]. Oral contraceptives (OCs) prevent pregnancy primarily by suppressing ovulation through the combined action of estrogen and progestin. Ovulation is inhibited by the suppression of luteinizing hormone (LH), so called progesto-

* Department of Obstetrics and Gynaecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

genic effect, and in part by the suppression of follicle stimulating hormone (FSH), as well as estrogenic effect(1,2).

There has been a continuing trend to reduce the dose of both estrogen and progestin. The commonly used formula is a preparation containing 20 micrograms (mcg) of ethinyl estradiol (EE) and 75 mcg of gestodene (GS). Fear that further lowering of the estrogen dose might compromise contraceptive reliability appears unfounded, and both studies on follicular development and clinical studies suggest that the dose provides effective contraception(3-5).

Numerous studies have demonstrated that during the "pill free" week, there is a progressive rise of 10-12 mm coincidental to the rise in the concentration of FSH and LH(6-10). If the start of OCs is delayed even by a single day, there is an increased risk of continued follicular growth and ovulation(11). Large follicles have a potentiality to ovulate in response to LH surge; contraceptive effect depends on the suppression of the LH surge and/or disruption of endometrial cycle(12). Therefore, OCs containing 20 mcg of EE on the first day and not later than the fifth day of their period is recommended. Some clinical data suggest a return of significant activity of ovarian follicle and an increased risk of the ovulation during a longer, but customary, 7-day period of pill free interval(13).

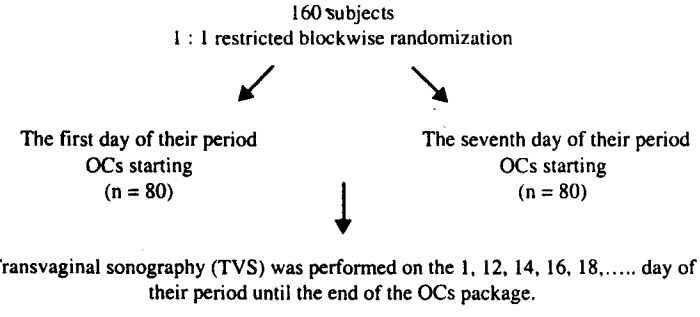
From the authors' experience in family planning services, however, many users failed to start on their first day and even began later than their fifth period day. So far to our knowledge, there has been no report on the influence of starting OCs containing 20 mcg EE on the seventh day of their period on ovulation. The objective of this study was to compare ovulation during the first day and the seventh day of their period starting OCs containing 20 mcg EE and 75 mcg GS.

MATERIAL AND METHOD

This randomized, clinical trial was carried out at the Family Planning Clinic of King Chulalongkorn Memorial Hospital, Bangkok, Thailand. In all, 160 healthy women who were between 23 and 44 years of age, who had regular cycles, and were not using any type of OCs steroid. All subjects were required to have a body mass index (BMI) of 18-24 kg/m^2. The exclusion criterias were namely : pregnancy, abnormal uterine bleeding, history of liver disease, breast cancer or pelvic organs cancer, myoma uteri and history of coagulation defect. Subjects were randomized into one of two study groups at 1 : 1 ratio by a restricted blockwise randomization. Subjects received one package of OCs containing 20 mcg EE and 75 mcg GS (Meliane, Schering, Germany). The first group started OCs on the first day of their period and the other group on the seventh day of their period. All subjects had pelvic sonography performed with a 5 MHz. vaginal probe and a CAPASEE III (Ultrasound diagnostic system, TOSHIBA) machine on the 1, 12, 14, 16, 18, ... day of their period until the end of the OCs package to detect the presence of growth and outcome of a dominant follicular like structure (FLS). Both ovaries were visualized during every sonographic examination, and the maximum diameters of all follicles were measured in three planes. All subjects had pelvic sonography performed by a sonographer (researcher). The study was approved by the Ethical Committee of the Faculty of Medicine, Chulalongkorn University.

Design

To detect an expected difference in ovulation rate between the groups of 10 per cent at an alpha level of 0.05 with a power of 80 per cent, a samples size of 144 (72 per group) would be required. Allowing for a dropout rate of 10 per cent, the authors aimed to recruit 160 subjects (80 per group).



Assesment

The endpoint was the ovulation rate during OCs use. Ovulation was defined as the dominant FLS detected by TVS and followed-up every other day until its collapse occurred. The user's compliance was monitored by a daily checkcard and all adverse effects were collected.

Statistical analysis

The main analysis was the difference in the ovulation rate between the two groups; 95 per cent confidence interval (CI) was calculated to determine the difference between the group that started on the first day *vs* the group that started on the seventh day of their period. The level of significance was determined by Fisher's exact test.

RESULTS

In all, 77 of 80 subjects were randomized to start the OCs on the first day of their period and 78 of 80 subjects, randomized to start OCs on the seventh day of their period, completed the study, and yielded a total of 155 treatment cycles. All subjects reported no adverse effects of OCs containing 20 mcg EE. The mean age of the subjects who started on the first day of their period was 33 ± 2.5 years, and who started on their seventh day of their period was 31 ± 3.0 years. The mean parity was 2 ± 0.5 and 2 ± 0.7 for those in the first and seventh day of their period respectively. The mean BMI of those who started on the first day of their period was 23 ± 1.5 kg/m^2 and in the latter was 21 ± 2.0 kg/m^2. There were no significant differences between any of these parameters (Table 1). A total 8 of 78 subjects in the seventh day group had enlarged FLS which later collapsed and were defined as ovulation (Fig. 1). There were 4 of 78 subjects in the seventh day group was had persistant enlarged FLS until the end of the package (Table 2).

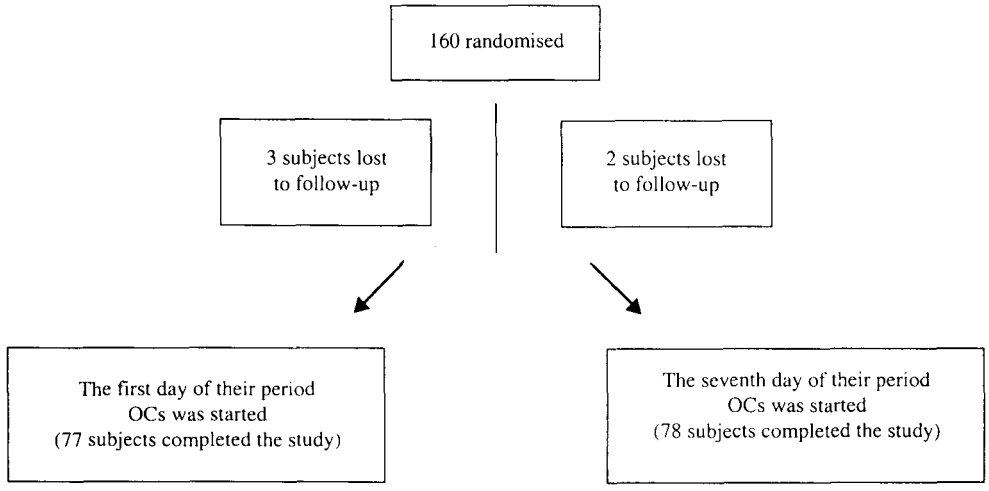


Table 1. Demographic datas.

Group Demo-graphic data	The first starting day group (Mean ± SD)	The seventh starting day group (Mean ± SD)	P-value
Age	33 ± 2.5	31 ± 3.0	0.07
BMI (kg /m^2)	23 ± 1.5	21 ± 2.0	0.08
Parity	2 ± 0.5	2 ± 0.7	0.08

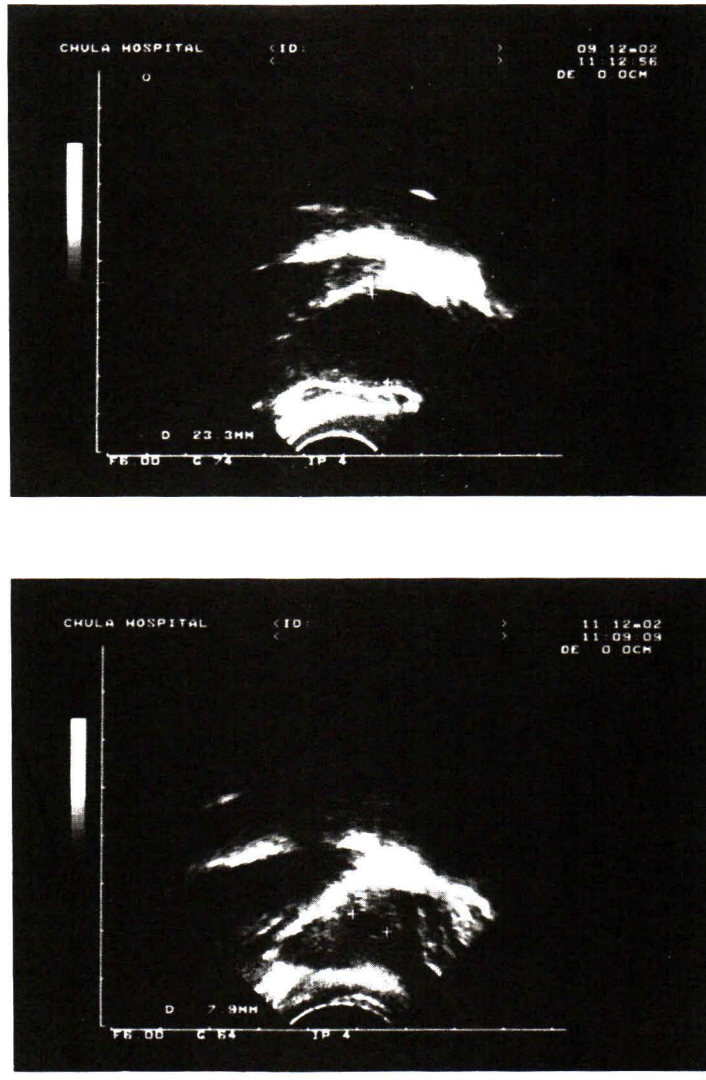


Fig. 1. Enlarged and collapsed FLS.

DISCUSSION

The effect of OCs on follicular activity is mainly estrogen dependent, which has been progressively reduced from 150 mcg mestranol that was present in the original Enovoid. The dose in modern low dose, combined OCs 20 mcg EE is probably the minimum that reliably and sufficiently suppresses FSH to prevent the growth of ovulatory follicle. If the start of the OCs containing 30 mcg EE is delayed by a single day (until day 8), there is a risk of continued follicular growth and ovulation[11] which means the start of OCs containing 30 mcg EE can be extended to the seventh day of their period which can still significantly prevent the growth of ovulatory follicle. However, there is no solution to the impact of starting on the seventh day of their period on ovarian follicular activity in 20 mcg EE OCs.

In this comparative study, starting 20 mcg EE and 75 mcg GS on the seventh day of their period was found to have a statistically significant number of ovulation when compared to starting on the first day of their period. Inhibition of ovulation is the principal mechanism through which progestin provides a contraceptive effect. Progestational agents primarily

Table 2. Clinical data of the study.

Group Ovulation	The first starting day group	The seventh starting day group	Fisher's exact test
Occurred	0	8	
Inhibited	77	70	p = 0.006
Total	77	78	

suppress luteinizing hormone (LH) secretion, therefore, they prevent LH surge which is needed for ovulation. In contrast, estrogenic compounds act centrally by suppressing FSH secretion and thereby prevent folliculogenesis.

Delaying the starting day of OCs cannot suppress FSH, which results in the growth of dominant follicle which later produces ovulation. The diameter of 13 mm was chosen as the criterion for the dominant follicle, because this is the maximum size associated with subsequent ovulation[14]. However, the dose of progestin is sufficient to suppress LH surge, which inhibits ovulation. The minimal sufficient dose of gestodene that inhibits ovulation is 40 mcg[15].

In the group that started on the seventh day of their period, the authors found 8 in 78 cases that escaped folliculogenesis and ovulation occurred, when compared to the group that started on the first day, there was a statistical significance (p = 0.006) which showed that estrogen does not inhibit FSH, allowing folliculogenesis and gestodene not to inhibit ovulation before LH surge in the cycle. Users of OCs containing 20 mcg had a significant ovulation when they started the package on the seventh day of their period, while users of OCs containing 30 mcg EE could start the package on the seventh day of their period without escaping ovulatory follicle. This results is beneficial information to cope with users of OCs containing 20 mcg EE to delay starting package problems.

SUMMARY

Starting 20 mcg EE and 75 mcg GS on the seventh of their period had statistical significance on the ovulation when compared to starting 20 mcg EE 75 mcg GS (p = 0.006) on the first day of their period.

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การศึกษาเปรียบเทียบแบบสุ่มถึงผลของวันเริ่มรับประทานยาเม็ดคุมกำเนิดชนิดฮอร์โมนรวมแบบขนาดยาต่ำต่อการเจริญของฟองไข่

สมเกียรติ สีตวาริน, พบ,*
อรรณพ ใจสำราญ, พบ, MHS, สุรศักดิ์ ฐานีพานิชสกุล, พบ, MPH**

บทความนี้เป็นการรายงานผลการศึกษา ผลลัพธ์ของการเริ่มยาคุมกำเนิดชนิดกิน (OCs) ซึ่งมีพิกัดยาต่ำมาก คือ ethinyl estradiol (EE) ขนาด 20 microgram (mcg) และ 75 mcg gestodene (GS) ซึ่งผลิตโดยบริษัท Meliane, Schering, ประเทศเยอรมนี โดยวิธีสุ่มตัวอย่างเป็นกลุ่ม (blockwise randomization) อาสาสมัครหญิงผู้มีสุขภาพแข็งแรง และมีรอบเดือนปรกติ และไม่มีประวัติเคยได้รับยาคุมกำเนิดชนิดที่มีสเตียรอยด์มาก่อน จำนวนทั้งสิ้น 160 คน ซึ่งมีอายุอยู่ระหว่าง 23-44 ปี และเข้ามารับบริการวางแผนครอบครัว ณ คลินิกวางแผนครอบครัว โรงพยาบาลจุฬาลงกรณ์ โดยอาสาสมัครเหล่านี้ถูกแบ่งออกเป็นสองกลุ่ม ๆ จำนวน 80 คน เท่ากัน (อัตราส่วน 1 ต่อ 1) และอาสาสมัครแต่ละคนได้รับยาคุมกำเนิดคนละหนึ่งกล่อง และกำหนดให้อาสาสมัครในกลุ่มหนึ่งเริ่มต้นกินยาในวันแรกของรอบเดือน ส่วนอีกกลุ่มหนึ่งเริ่มกินยาในวันที่เจ็ดของรอบเดือน ในระหว่างกินยาคุมกำเนิดอยู่นี้ผู้วิจัยทำการเก็บของมูลการเปลี่ยนแปลงที่เกิดขึ้นที่รังไข่โดยการตรวจทางคลื่นเสียงความถี่สูงผ่านทางช่องคลอด (transvaginal sonography หรือ TVS) วันเว้นวัน เพื่อติดตามการเปลี่ยนแปลงของขนาดสิ่งปรากฏคล้ายถุงน้ำในรังไข่ (follicular-like structure หรือ FLS) เพื่อศึกษาวันที่ถุงน้ำยุบตัวแฟบลง ซึ่งเป็นการแสดงการตกไข่ ที่เกิดขึ้นในกลุ่มทั้งสอง ผลการวิจัยพบว่าจำนวนการตกไข่ในกลุ่มที่กินยาในวันที่หนึ่งมีจำนวน 0 ราย และกลุ่มที่เริ่มในวันที่เจ็ดมีจำนวน 8 ราย ซึ่งแสดงความแตกต่างอย่างมีนัยสำคัญทางสถิติ ($p = 0.006$) ผลการวิจัยนี้จะเป็นประโยชน์ในการให้คำแนะนำสตรีที่กินยาคุมกำเนิดช้ากว่ากำหนด

คำสำคัญ : ยาคุมกำเนิดชนิดกิน, ถุงน้ำในรังไข่, รังไข่

สมเกียรติ สีตวาริน, อรรณพ ใจสำราญ, สุรศักดิ์ ฐานีพานิชสกุล
จดหมายเหตุทางแพทย์ ฯ 2546; 86: 442-448

* ภาควิชาสูติศาสตร์-นรีเวชวิทยา, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ ฯ 10330