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Greater inhibition of the pituitary–ovarian axis in oral contraceptive regimens with a shortened hormone-free interval

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Abstract

Objective: Our objective was to test the hypothesis that shortening the hormone-free interval (HFI) between cycles of 21 days of oral contraceptives (OCs) reduces pituitary secretion of gonadotropins and ovarian production of estradiol and inhibin-B.

Design: We used a prospective trial design comparing the standard 7-day HFI and shortened HFI during cycles, with an OC containing 0.03 mg of ethinyl estradiol and 3 mg of drospirenone.

Methods: Twelve current OC users initially utilized an OC in the standard fashion, with 21 days of active pills and a 7-day HFI, followed by 21 days of active pills with randomization to either a 3-day or a 4-day HFI. Nine daily blood samples were obtained for the measurement of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol and inhibin-B, beginning with active pill 21 days before each HFI of the two cycles. Analysis of variance was used to compare hormones for 9 days bracketing the standard 7-day HFI and to compare, within individuals, the 7-day HFI and the subsequent shortened HFI.

Results: During the 7-day HFI, all four hormones significantly ($p>.001$) increased from baseline. FSH increased beginning on HFI Day 4, inhibin-B increased beginning on HFI Day 5, and LH and estradiol increased beginning on HFI Day 6. Subjects randomized to the 3-day or the 4-day HFI did not differ with regard to age and body size ($p=.88$) or initial hormone level ($p=.67$). Greater pituitary and ovarian suppression was seen with the shortened HFI for all four hormones ($p<.001$). Hormone levels in the 7 days after the last active pill of the second cycle did not differ ($p>.4$) between the 3-day and the 4-day HFI groups.

Conclusions: Shortening the HFI from 7 days to 3 or 4 days blunts increases in the pituitary–ovarian axis during cycles of OC use.

Keywords: Oral contraceptives; LH; FSH; Estradiol; Inhibin-B

1. Introduction

Oral contraceptives (OCs) are the most commonly used method of reversible contraception, with the majority of women using them sometime during their reproductive life. Modifications have primarily involved lowering hormone content and utilizing new progestin components. The same basic design of 21 hormone-containing pills and a 7-day hormone-free interval (HFI) was the standard, until the recent approval of an extended regimen (Seasonale®; Barr Laboratories, Ponoma, NY, USA). The 21/7-day regimen was arbitrarily created to mimic the average spontaneous menstrual cycle of 28 days.

Although OCs are very effective in preventing pregnancy, studies have confirmed an incomplete suppression of ovarian function with follicular growth and resultant endogenous hormone production and potential for follicular cysts [1–3]. Additionally, Sulak et al. [4] confirmed that an HFI of 7 days induces monthly withdrawal symptoms of bleeding, pain, breast tenderness, bloating/swelling and increased use of pain medications. This study evaluates the serum levels of four reproductive hormones during the HFI

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to determine whether the pituitary–ovarian response can be blunted by decreasing the HFI from the standard 7 days to either 3 or 4 days.

2. Methods

This prospective study was approved by the Scott and White Institutional Review Board. The study population consisted of women who were currently on OCs and have been on OCs for a minimum of 3 months, with no contraindications to continued use. The mean age was 29 years (range, 25–42 years of age), and the mean body mass index (BMI) was 22.7 kg/m^2 (Table 1). Exclusion criteria included age of >50 years, smoking and BMI>35 kg/m^2. Fourteen patients were initially enrolled, but two dropped out prior to completion of the initial 21 days of OCs. One patient discontinued participation in the study due to an unexpected movement out of the area, and another quit due to extreme breast tenderness resulting from the OC.

The 12 subjects all used a monophasic OC containing 30 μg of ethinyl estradiol and 3 mg of drospirenone (Yasmin®; Berlex Laboratories, Wayne, NJ, USA). Participants completed one baseline 21/7 cycle of the study OC and then were followed through two successive HFIs with hormone evaluations. The initial hormone evaluation cycle was taken in the standard fashion with 21 active pills and a 7-day HFI, immediately followed by a second cycle with 21 active pills and a shortened 3- or 4-day HFI. Six patients were randomized to a 3-day HFI using a sealed envelope system, and six patients were randomized to a 4-day HFI. All subjects resumed active pills following the shortened HFI. This design allowed comparisons within patients for standard and shortened HFI, and comparisons between subjects for 3- versus 4-day HFI. Two separate sets of nine consecutive daily blood draws were obtained, each starting on the last active pill day (Day 21) of each cycle and continuing through the entire HFI into the next cycle. Daily blood samples were processed for sera that were frozen below 60°C until grouped for assay to measure follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol and inhibin-B. Samples were grouped so that all of each subject's samples were included in the same assay to minimize assay variation.

Table 1
Patient characteristics reported as least squares means (S.E.)

Characteristics	Patient assigned to the 3-day HFI group (N=6)	Patients assigned to the 4-day HFI group (N=6)
Weight (lb)	136 (8)	137 (8)
Height (in.)	65 (1)	65 (1)
BMI (kg/m^2)	22.5 (1.4)	22.9 (1.4)
Age (years)	27.4 (2.2)	30.2 (2.2)
Cycle with 7-day HFI		
Initial LH (mIU/mL)	0.9 (0.5)	0.5 (0.5)
Initial FSH (mIU/mL)	1.0 (0.5)	1.0 (0.5)
Initial estradiol (pg/mL)	10 (4)	11 (4)
Initial inhibin-B (pg/mL)	3 (2)	3 (2)
Cycle with variable HFI		
Initial LH (mIU/mL)	1.4 (0.9)	0.9 (0.9)
Initial FSH (mIU/mL)	1.7 (0.9)	1.5 (0.9)
Initial estradiol (pg/mL)	15 (5)	24 (5)
Initial inhibin-B (pg/mL)	2 (2)	3 (2)

No significant (p=.88) difference between groups for body size and age, using Wilks multivariate test.
No significant (p=.67) difference between groups for initial hormone measures, using Wilks multivariate test.

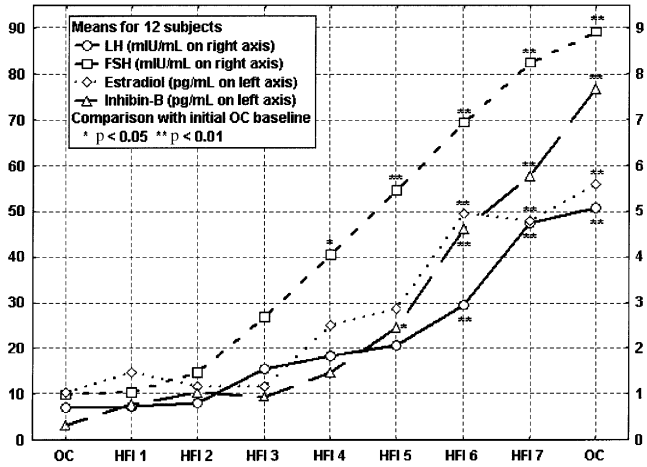

Fig. 1. Means of LH, FSH, estradiol and inhibin-B during a 9-day interval from the last day of active OC to 7 days of HFI and the first day of active OC of the next cycle for 12 patients utilizing a standard 21/7 regimen of OC containing 0.03 mg of ethinyl estradiol and 3 mg of drospirenone.

Estradiol, LH and FSH assays were performed using the AVIDIA Centaur instrument (Bayer HealthCare LLC, Tarrytown, NY, USA). The assay is a chemiluminescence immunoassay. The tests were performed in duplicate, as per the manufacturer's instructions. Gonadotropins were standardized to the World Health Organization Second International Standards (human LH-IS 80/552 and human FSH-IS 94/632). Controls were run on a routine basis with interassay and intra-assay coefficients of variation (CVs) of <6%. The minimum detectable levels were 0.09 mIU/mL, 0.3 mIU/mL and 15 pg/mL, respectively, for LH, FSH and estradiol. Results are reported as picograms per milliliter for estradiol and as milli international units per milliliter for FSH and LH. Ethinyl estradiol is not detectable in the estradiol assay. Dimeric inhibin-B was assayed in duplicate by enzyme-linked immunosorbent assay following the manufacturer's instructions, with kits provided by Diagnostic System Laboratories, Inc. (Webster, TX, USA). Results are reported in picograms per milliliters, with interassay and intra-assay CVs of between 8% and 18%. The minimum detectable level was 10 pg/mL.

Repeated-measures analysis of variance was used to compare hormone levels within 9 days bracketing the standard 7-day HFI. These methods were also used for comparing the 7-day HFI and the subsequent shortened HFI within individuals. Post hoc comparisons were made using Newman–Keuls test. $p<.05$ was set as statistically significant.