

Activity of the Pituitary-Ovarian Axis in the Pill-Free Interval During Use of Low-Dose Combined Oral Contraceptives

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This study was performed to evaluate pituitary-ovarian recovery in the pill-free interval during use of three low-dose combined oral contraceptives (COC). Either the estrogen component or the progestin component was comparable in the study groups, to evaluate their relative influence. Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E_2) levels were measured and follicle number and size estimated by transvaginal sonography daily during the 7-day pill-free interval in 44 healthy volunteers using three different low-dose oral contraceptives. Healthy volunteers were enrolled using 20 μ g ethinyl estradiol (EE) + 75 μ g gestodene (GSD) (Harmone[®], Wyeth-Lederle; $n = 15$), 20 μ g EE + 150 μ g desogestrel (DSG) (Mercilon[®], Organon $n = 17$), or 30 μ g EE + 150 μ g DSG (Marvelon[®], Organon, $n = 12$) given according to the usual regimen of one tablet daily during 3 weeks and 1 week pill-free interval.

No ovulations were observed. Pituitary hormones were not statistically significantly different at the beginning of the pill-free interval between the study groups. FSH concentrations were significantly higher at the end of the pill-free interval in the 30 μ g EE group compared with both 20 μ g EE groups (7.0 [0.6–12.4] IU/L vs 4.9 [1.4–6.1] IU/L and 4.5 [2.4–7.4] IU/L; $p = 0.001$). In both 20 μ g EE groups, a single persistent follicle (24 and 28 mm) was present in one subject. Follicle diameters were statistically significantly smaller at the beginning and at the end of the pill-free period in the 30 μ g EE group compared with both 20 μ g EE study groups. Dominant follicles (defined as follicle diameter ≥ 10 mm) were observed at the end of the pill-free interval in both 20 μ g EE groups (in 27% and 18%

of women, respectively) but not in the 30 μ g EE group. Finally, the area-under-the-curve for E_2 was statistically significantly lower in the 30 μ g EE group compared with both 20 μ g EE groups.

In conclusion, the EE content rather than the progestin component in the studied COC determined the extent of residual ovarian activity at the beginning of the pill-free interval. Dominant follicles were encountered only in the 20 μ g EE study groups. CONTRACEPTION 1999;59:237–243 © 1999 Elsevier Science Inc. All rights reserved.

KEY WORDS: ovarian activity, pill-free period, follicle development, oral contraception, follicle stimulating hormone, estradiol

Introduction

The contraceptive effect during the use of combined oral contraceptives (COC) is predominantly established as a result of inhibition of the hypothalamic-pituitary-ovarian axis. Follicle growth is prevented and ovulation inhibited. The estrogen component is considered to inhibit follicle stimulating hormone (FSH) production and consequently to diminish FSH-dependent follicle growth. Should, however, a dominant follicle emerge, inhibition of the luteinizing hormone (LH) surge and thus ovulation is prevented through the progestin component. The progestin component alone does not seem to have a prominent effect on basal concentrations of LH and FSH but, notably, inhibits peak concentrations.¹ Although not completely understood, inhibitory effects of both components in COC are established through synergistic interactions at the hypothalamic-pituitary level.^{2,3}

The 7-day pill-free period of most currently used regimens allows for withdrawal bleeding and serves the purpose of mimicking the normal menstrual cycle. In addition, it allows reduction of the overall amount of steroids administered over a 4-week pe-

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riod. During the pill-free interval, pituitary-ovarian activity is allowed to resume in the absence of inhibitory steroids until the next medication strip is initiated. Numerous publications have described recovery of ovarian activity during the pill-free interval or after pill omissions.^{4,5} However, daily blood sampling together with ultrasound has rarely been performed. Few data are available to determine whether the magnitude of pituitary-ovarian suppression significantly differs among users of various low-dose COC. The present study compared resumption of pituitary-ovarian activity in women using three different low-dose COC to determine: 1) the maximum extent of suppression at the beginning of the pill-free interval, 2) the magnitude of recovery of pituitary-ovarian activity during the pill-free interval, and 3) the extent of pituitary-ovarian activity at the end of the pill-free interval, a starting point for the next cycle.

Materials and Methods

Subjects and Study Protocol

A total of 44 women using low-dose oral contraception were included in this single-center group comparative study in healthy female volunteers. The human ethics committee of the Dijkzigt Academic Hospital approved the study and all women gave written informed consent. The study was conducted according to the Declaration of Helsinki and the Good Clinical Practice (GCP) recommendations of the European Committee. Inclusion criteria were: age between 18 and 39 years; weight between 50 and 75 kg; and cycle length between 24 and 35 days before starting the use of oral contraceptives. Excluded were women with hyperprolactinemia or polycystic ovary syndrome, contraindications for the use of oral contraception, or any relevant medical disorder. Each volunteer entered the study on the first day of the pill-free period after the correct use of at least two cycles of study medication.

Three low-dose COC were used for comparison: Fifteen women used 20 µg ethinyl estradiol (EE) + 75 µg gestodene (GSD) (Harmonet, Wyeth-Lederle, Hoofddorp, the Netherlands), 17 women used 20 µg EE + 150 µg desogestrel (DSG) (Mercilon, NV Organon, Oss, the Netherlands) and 12 women used 30 µg EE + 150 µg DSG (Marvelon, NV Organon, Oss, the Netherlands). Thirty-two women were randomly allocated to receive either 20 µg EE + 150 µg DSG or 20 µg EE + 75 µg gestodene (GSD). Each subject was assessed in the pill-free period of the second cycle. The remaining 12 women using 30 µg EE + 150 µg DSG were enrolled while using the study medication

Assessments

All sonographic measurements were performed by a single investigator (A.M.vH.) using a 6.5 MHz transvaginal probe (Hitachi, Tokyo, Japan). Ovarian activity was assessed by counting the number of follicles after scanning each ovary from the inner to the outer margin in a longitudinal cross-section, as previously described.^{6,7} The diameter was taken to be the mean of the size of the follicle in a longitudinal and an anteroposterior plane. Beyond a diameter of 10 mm, measurements in three planes were performed. Follicles ≥ 10 mm were considered dominant.⁶⁻⁸ On every occasion, endometrial thickness was assessed as the maximum thickness (both sides) present in the longitudinal plane.

Serum samples were centrifuged within 2 h after collection. Serum E₂ levels were measured by radioimmunoassay (Diagnostics Products Corporation, Los Angeles, CA). Serum FSH and LH levels were determined by immunoradiometric assay (Delfia kits, Kabi Pharmacia, Türkü, Finland). Intra-assay and inter-assay coefficients of variation (CV) were <4.0% and <6.4% for FSH, <15.5% and <14.1% for LH, and <15% and <18% for E₂, respectively. Samples from one individual were run in the same assay.

Data Analysis

Results are presented as median and range unless stated otherwise. Study parameters were compared using the Mann-Whitney U-test, a nonparametric test for comparison of two independent groups. Differences were considered to reach statistical significance when $p < 0.05$.

Results

All 44 volunteers completed the study. Age, weight, and body mass index were not statistically significantly different among the study groups (data not shown). All women did use the studied COC for ≥ 2 months before the assessments in this study and there were no pill omissions reported. Figures 1, 2, and 3 show the study parameters throughout the pill-free interval. Table 1 shows pituitary-ovarian activity at the beginning and end of the pill-free interval as well as parameters for the entire period.

Pituitary activity

In both 20 µg EE groups, a significant rise in serum FSH and E₂ was observed from day 3 of the pill-free period onward ($p < 0.01$, Wilcoxon signed rank test). In the 30 µg EE group, this occurred from day 4

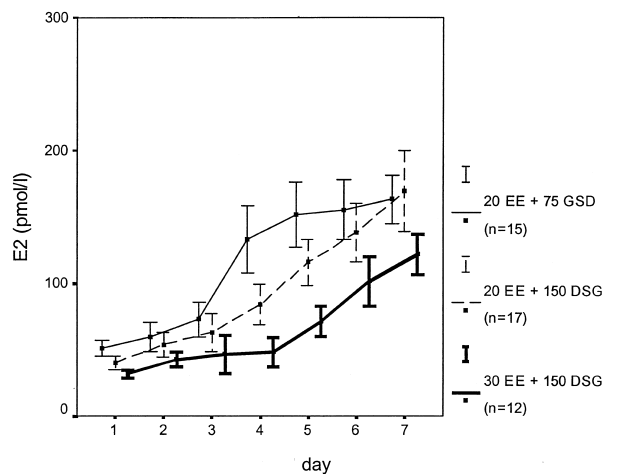
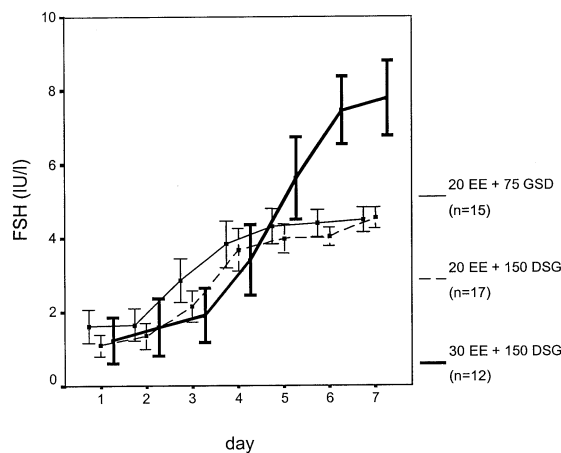
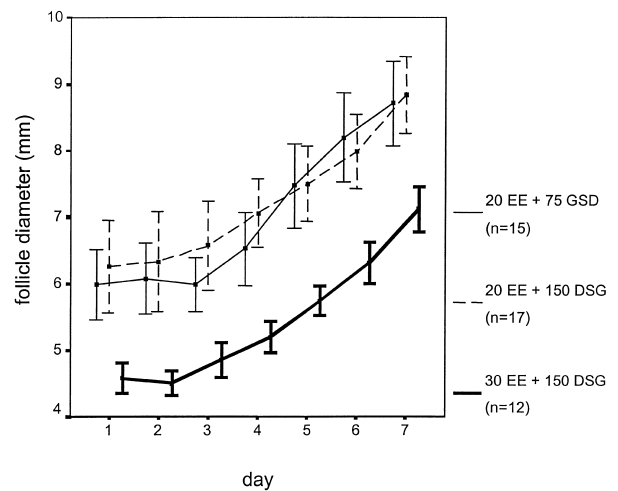
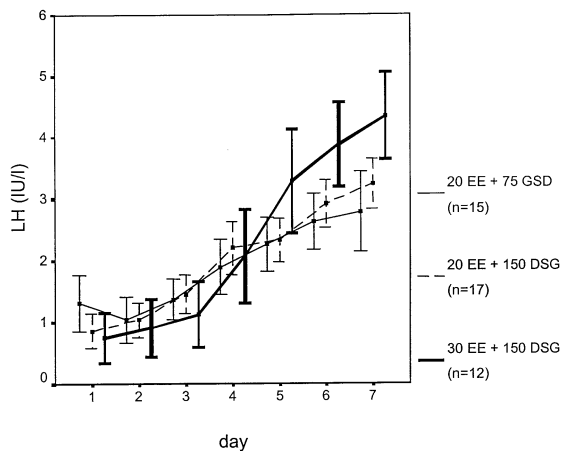


Figure 1. Daily serum concentrations (IU/L) of LH (upper panel) and FSH (lower panel) during the pill-free period (days 1-7) in 44 healthy volunteers using three different combined oral contraceptive regimens. Data are presented as mean \pm SE.

Figure 2. Daily maximum follicular diameters (mm) (upper panel) and serum concentrations of E₂ (pmol/L) (lower panel) during the pill-free period (days 1-7) in 44 healthy volunteers using three different combined oral contraceptive regimens. Data are presented as mean \pm SE.

20 μ g EE + 150 μ g DSG versus 20 μ g EE + 75 μ g GSD

LH and FSH concentrations at the beginning (day 1) of the pill-free interval and at the end of the pill-free interval (day 7) were not significantly different. The area-under-the-curve (AUC) for both hormones was calculated as a measure for the total amount of hormone produced during this period. These were also not statistically significantly different.

the different shape of the FSH concentrations in both groups, the AUC for FSH and LH was not different.

20 μ g EE + 150 μ g DSG versus 30 μ g EE + 150 μ g DSG

Both LH and FSH concentrations were comparable on day 1. On day 7, FSH concentrations were statistically higher in 30 μ g EE + 150 μ g DSG users (4.5 [2.4-7.4]

Ovarian Activity

No ovulation was observed in either group. In both 20 μ g EE study groups, one volunteer with a persistent follicle was seen throughout the pill-free interval, ranging from 23.9 mm to 20.6 mm in the 20 μ g EE + 75 μ g GSD group and 27.6 mm to 26.3 mm in the 20 μ g EE + 150 μ g DSG group. Because both structures were accompanied by low E₂ concentrations, they were omitted from comparative analysis and replaced by diameters from the second largest follicle present. A follicle \geq 10 mm was present at the end of the pill-free interval in 4 of 15 women (27%) in the 20

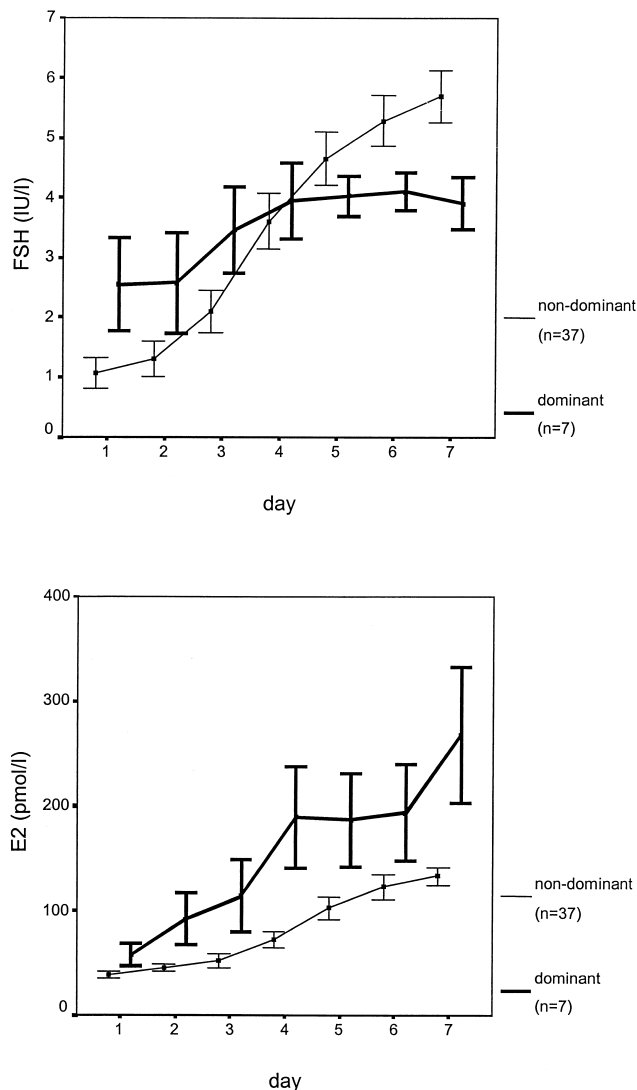


Figure 3. Daily serum concentrations of FSH (IU/L) (upper panel) and serum concentrations of E₂ (pmol/L) (lower panel) during the pill-free period (days 1–7) in women who either have or do not have a dominant follicle present at the end of the pill-free period. Data are presented as mean \pm SE.

in the 20 μ g EE + 150 μ g DSG group, whereas in the 30 μ g EE + 150 μ g DSG group no follicles \geq 10 mm were found. These differences were not statistically significant (Fisher's exact test).

20 μ g EE + 150 μ g DSG versus 20 μ g EE + 75 μ g GSD

Maximum follicle diameters did not differ statistically significantly at the start of the pill-free interval in the two 20 μ g EE groups. Follicular growth of the largest follicle during the pill-free interval was similar in both groups: 2.9 mm (–3.0–7.1 mm) and 2.6 mm

20 μ g EE + 75 μ g GSD users, respectively. Finally, follicle diameters of the largest follicle present at the end of the pill-free interval were also not statistically different. E₂ concentrations did not differ statistically significantly on day 1 or day 7 between the two groups. The AUC for E₂ was also not different.

20 μ g EE + 150 μ g DSG versus 30 μ g EE + 150 μ g DSG

On day 1 of the pill-free interval, maximum follicle diameters were smaller in the 30 μ g EE + 150 μ g DSG group, compared with the 20 μ g EE + 150 μ g DSG group ($p = 0.01$). This difference was still present at the end of the pill-free interval ($p = 0.02$). Follicle growth was not different in the two groups: 2.9 mm (–0.2–7.0 mm) and 2.6 mm (–0.3–4.7 mm) for 30 μ g EE + 150 μ g DSG and 20 μ g EE + 150 μ g DSG, respectively. E₂ concentrations did not differ on days 1 and 7 but the AUC for E₂ was just significantly higher in the 20 μ g EE group ($p = 0.05$).

The correlation between FSH concentrations and LH concentrations on day 1 of the pill-free interval was consistent throughout different medication groups (Pearson's $r = 0.78$, $p = 0.0001$). However, other correlations were less powerful: E₂ and follicle diameter (Pearson's $r = 0.49$, $p = 0.001$), FSH and E₂ (Pearson's $r = 0.34$, $p = 0.02$), and E₂ and LH (Pearson's $r = 0.34$, $p = 0.02$). At the end of the pill-free interval, the strongest correlation was found between follicle diameter and E₂ concentration (Pearson's $r = 0.61$, $p = 0.001$). Follicle growth correlated weakly with the AUC-FSH during the pill-free interval (Pearson's $r = 0.32$, $p = 0.03$).

The presence of a dominant follicle at the end of the pill-free period was statistically significantly correlated with FSH on day 1 ($p = 0.05$), with E₂ on day 1 ($p = 0.05$), and with follicle diameter on day 1 ($p = 0.01$), but not with the study medication or EE dosage.

Discussion

During the luteal-follicular transition of the normal menstrual cycle, FSH levels surpass the threshold for stimulating ovarian activity. This intercycle rise in FSH elicits recruitment of a cohort of synchronous follicles from which a single dominant follicle is selected later in the follicular phase of the cycle.⁵

Conventional combined oral contraceptives act primarily through inhibition of follicular growth in combination with peripheral progestin effects. In any situation in which medication is discontinued (either through "missing the pill" or a scheduled cessation of medication in the pill-free interval), recovery of pituitary-ovarian activity has been documented.^{9–14} In

Table 1. Endocrine and ultrasound characteristics during the pill-free period in three low-dose, combined oral contraceptives users

| Assessments | | 20 µg EE + 75 µg GSD | | 20 µg EE + 150 µg DSG | | 30 µg EE + 150 µg DSG | | p‡ |
|-------------------------------|----------|-------------------------|-----------|--------------------------|-----------|--------------------------|----------|-------|
| | | Median/Range | p* | Median/Range | p† | Median/Range | p‡ | |
| LH (IU/l) | day 1 | 0.7 | 0.05-6.2 | 0.2 | 0.05-3.7 | 0.14 | 0.05-4.6 | 0.02 |
| | day 7 | 2.5 | 0.05-11.0 | 3.0 | 0.3-6.5 | 4.1 | 0.1-9.6 | |
| | AUC 1-7 | 12.5 | 1.2-41.8 | 10.3 | 3.9-34.6 | 12.9 | 0.4-46.4 | |
| FSH (IU/l) | day 1 | 1.0 | 0.05-5.4 | 0.6 | 0.05-3.9 | 0.28 | 0.05-6.1 | 0.001 |
| | day 7 | 4.9 | 1.4-6.1 | 4.5 | 2.4-7.4 | 7.0 | 0.6-12.4 | |
| | AUC 1-7 | 22.6 | 4.5-40.3 | 20.9 | 11.0-32.9 | 26.5 | 1.0-60.2 | |
| Max. fol. diameter (mm) | day 1 | 5.6 | 3.9-10.7§ | 5.2 | 4.0-15.2# | 4.5 | 3.5-6.3 | 0.05 |
| | day 7 | 7.9 | 5.4-14.4§ | 8.3 | 5.5-14.9# | 7.2 | 5.2-9.0 | |
| | day 1-7† | 2.9 | -3.0-7.1 | 2.6 | -0.3-4.7 | 2.9 | -0.2-7.0 | |
| E ₂ (pmol/l) | day 1 | 55 | 12-97 | 37 | 14-90 | 29 | 20-52 | 0.02 |
| | day 7 | 161 | 82-315 | 167 | 68-622 | 116 | 43-214 | |
| | AUC 1-7 | 661 | 343-1612 | 567 | 293-2153 | 387 | 295-907 | |

Areas-under-the-curve (AUC) were calculated for endocrine assessments; the increase of the maximum follicular diameter is given for sonographic assessments

Statistical differences were calculated between group 1 and 2 (p*), group 2 and 3 (p†), and group 1 and 3 (p‡).

† follicular growth from day 1 until day 7

§ In 1 patient, a persistent follicle was excluded (23.9 mm on day 1, 20.6 mm on day 7).

In 1 patient, a persistent follicle was excluded (27.6 mm on day 1, 26.3 mm on day 7).

pituitary-ovarian activity should remain suppressed to an extent that the development of dominant follicles is prevented. These follicles carry the risk of ovulation or continued growth to become persisting follicles/cysts. The inhibitory effect of the contraceptive combination should, therefore, be sufficient to arrest and repress the amount of activity present at the end of the 7-day pill-free interval. However, little is known about the influence of contraceptive combinations or the relative importance of the estrogen and progestin component on the dynamics of pituitary-ovarian recovery during the pill-free interval. The present study focused on pituitary-ovarian activity during the pill-free interval with three low-dose COC. By comparing Mercilon (20 µg EE + 150 µg DSG) with either Marvelon (30 µg EE + 150 µg DSG) or Harmonet (20 µg EE + 75 µg GSD), the relative importance of the estrogen or progestin component was studied.

At the start of the pill-free interval, 20 µg EE-containing COC are expected to have a lesser degree of pituitary suppression compared with the 30 µg EE COC due to a dose-dependent effect on FSH secretion.¹⁵ Although serum gonadotropin concentrations at the beginning of the pill-free interval were markedly reduced in the 30 µg EE study group, no statistically significant differences were found in gonadotropin concentrations on the first day of the pill-free period between any of the study groups. This is probably largely due to interindividual variations in

sample size. The rate of pituitary recovery in the 30 µg EE group appeared to be different compared to both 20 µg EE groups; the increase of LH and FSH started more slowly but was more pronounced towards the end of the pill-free interval. FSH concentrations in the 30 µg EE group were statistically higher compared with both 20 µg EE groups at the end of the pill-free period (see Table 1). It remains speculative whether the higher dosage of EE in the 30 µg EE group can be held responsible for the continued FSH suppression during the first days of the pill-free period. Reduced ovarian feedback by hormones produced by early antral follicles such as E₂ and inhibin B may cause higher FSH levels at the end of the pill-free period in the 30 µg EE group.¹⁶

Despite the lack of major differences in FSH and LH levels during the pill-free interval between the study groups, an important difference in ovarian activity was noted. In both study groups using 20 µg EE COC, a persistent follicle >20 mm was observed at the beginning of the pill-free interval. Even when these were excluded from statistical comparison, maximum follicle diameters were significantly smaller in the 30 µg EE group. The growth rate of the maximum follicle present (as measured by the increase in maximum follicle diameter from day 1 to day 7) was not different between the study groups. No dominant follicles were seen in the 30 µg EE + 150 µg DSG group, whereas 18%-27% of women in both 20 µg EE group presented with dominant follicles. In three of

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