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REVIEW ARTICLE

Rationale for eliminating the hormone-free interval in modern oral contraceptives

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ABSTRACT

Background: Although most low-dose combined oral contraceptives (COCs) include 7-day hormone-free intervals (HFIs), these COCs could incompletely suppress ovarian activity. *Objectives:* To review the impact of HFIs on ovarian suppression and tolerability, and evaluate the utility of COCs without traditional 7-day HFIs. *Search strategy:* PubMed was searched for clinical studies published in English between January 1980 and April 2015 on the impact of HFIs and HFI modifications in COCs. *Selection criteria:* Articles assessing contraceptive efficacy or tolerability as the primary focus were included. *Data collection and analysis:* Abstracts of 319 articles were screened. *Results:* Analysis of the 161 articles selected revealed that suppression of ovarian activity with low-dose COCs with 7-day HFIs is suboptimal. Loss of ovarian suppression during 7-day HFIs is commonly associated with follicular development, and most dominant follicles appear during this period. By contrast, increased ovarian suppression was noted in regimens that shortened or eliminated the HFI, or that substituted low-dose ethinyl estradiol for the HFI. *Conclusions:* Extended regimens with modified HFIs might provide greater ovarian suppression with the potential for increased contraceptive effectiveness. Additional research is needed to evaluate whether COC regimens that include 10 μg ethinyl estradiol instead of an HFI might improve tolerability.

1. Introduction

When combined oral contraceptives (COCs) were introduced more than five decades ago, the 21/7 regimen (21 days of active pills, followed by a 7-day hormone-free interval [HFI]) was chosen in an effort to mimic women's monthly menstrual cycles and to reassure women that they were not pregnant [1,2]. Although refinements such as new progestogens, reduced doses of ethinyl estradiol (EE), the use of estradiol, and reduction or elimination of the HFI have been introduced in combined hormonal contraception, most COC users continue to take active pills for 21 days followed by a 7-day HFI. Evidence suggests, however, that 21/7 regimens might not completely suppress ovarian activity and ovarian development.

The primary aim of the present review was therefore to evaluate evidence regarding the potential impact of the 7-day HFI on ovarian activity, contraceptive effectiveness, and adverse effects. The impact of COC options with shorter HFIs or less frequently occurring HFIs as compared with traditional 21/7 regimens was also considered.

2. Materials and methods

In a structured review, PubMed was searched to identify studies on the impact of HFIs and modifications in HFIs in COCs that were published in English between January 1, 1980, and January 15, 2015. The last search date was April 30, 2015. The keywords used were "combined hormonal contraceptive," "oral contraceptive," "hormone-free interval," "ovarian suppression," "extended regimen," "ethinyl estradiol," and "hormone withdrawal." Articles were excluded if they did not evaluate the impact of HFIs on ovarian activity, contraceptive effectiveness, or adverse effects; or they did not consider regimens with modified HFIs. Reference lists of included studies were manually searched to identify additional papers.

3. Results

3.1. Search results

The abstracts of 319 articles were screened, and 161 articles underwent full-text review. The complete list of articles included in the analysis is provided in Supplementary Material S1.

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3.2. Limitations of the traditional 7-day HFI

COCs provide contraception by inhibiting the hypothalamic–pituitary–ovarian (HPO) axis, suppressing follicular growth, and inhibiting ovulation [3,4]. The primary role of the progestogen component of COCs is to prevent ovulation through a negative feedback mechanism that results in a decrease in luteinizing hormone (LH) [4]. Progestogen action also reduces the receptivity of cervical mucus and decreases endometrial thickness [4]. Estrogens contribute to the contraceptive mechanism of COCs by inhibiting both follicle-stimulating hormone (FSH) and LH. The inhibition of FSH seems to be related to estrogen dose and duration, because more follicular activity is seen with progestogen-only methods than with COCS, and with regimens with lower EE doses (<35 μg) than with those with higher EE doses [5,6]. Most COCs do not completely suppress ovarian follicular development [7,8].

A possible explanation for the incomplete ovarian suppression seen with today's COCs is the clearance of contraceptive steroid hormones during the HFI. In fact, evidence indicates that the hormonal events and follicular growth that take place during the HFI are similar to those seen early during the follicular phase of spontaneous menstrual cycles [7]. In the normal menstrual cycle, selection of the dominant follicle occurs within the first 7 days [1]. These physiologically selected dominant follicles secrete estradiol, which stimulates their maturation and inhibits the growth of subordinate follicles [8]. Dominant follicles (usually ≥10 mm) have the greatest potential to develop further and ovulate [9]. Among women using COCs, a loss of endocrine suppression during the HFI is associated with follicular development [1,6,8,10]. Indeed, evidence suggests that 86% of dominant follicles emerge during the 7-day HFI, irrespective of the regimen [8]. Women who initiate COC use after 7 days of follicle growth could already have a dominant follicle that can continue to develop and possibly ovulate [11].

Modern COCs may also provide incomplete ovarian suppression owing to their reduced estrogen dose. Early COCs contained estrogen doses as high as 150 μg. Although the lower EE doses in today's COCs (generally ≤35 μg) have improved safety and tolerability, accumulating evidence suggests that the decreasing EE doses could have compromised the degree to which COCs suppress HPO activity, particularly during the HFI [1,8].

Although the half-life of EE is constant irrespective of dose, its maximum concentration is related to dose and, because EE is cleared from the system 2–3 days after the final active pill, the threshold level at which recovery of the HPO axis and follicular growth can occur is achieved earlier with very low-dose EE pills [3,7]. It could take as long as 12 days to achieve steady-state estrogen and progestogen levels among obese women using COCs with a 7-day HFI [12], and follicular development could continue into the first week of the next cycle.

In a recent pilot study, Cho et al. [13] evaluated the impact of various 21/7 regimens during the 7-day HFI and found better suppression of pituitary and ovarian activity with 30- and 35-μg EE formulations on day 1 of the HFI as compared with regimens that included 20 μg EE. Mean levels of LH, FSH, and estradiol increased during the HFI in all regimens; at day 7, however, LH and FSH levels were similar among the groups. Maximum estradiol levels at day 7 were 477, 247, and 199 pg/mL for the 20-, 30-, and 35-μg EE doses, respectively [13].

Follicular development is also greater among women using COC regimens with 20 μg EE than among those using regimens with higher EE doses [3,6]. The reduced ovarian suppression observed with lower EE doses and long HFIs might be particularly relevant in clinical situations when a missed pill occurs early in the cycle following the HFI [1,12,14]. It is not uncommon to miss pills during the first week of the COC cycle. In one study [15], 23% of women using COCs reported missing a pill at least once during a 28-day cycle, and 42% of women who missed a pill did so during the first week of the cycle following the HFI.

The pharmacokinetics of COCs in obese women could differ from those in women of normal weight, which could lead to inadequate ovarian suppression and potentially to escape ovulation [14]. These pharmacokinetic differences are magnified in obese women using COCs with lower-dose EE formulations. Given the rapid increase in the prevalence of obesity, these differences in pharmacokinetics and their possible impact on ovarian suppression may have important implications for the effectiveness of COCs in the general population, although the true impact of weight versus non-compliance on oral contraceptive efficacy is debated [16].

Strategies to mitigate the impact of decreasing EE doses on ovarian suppression have been evaluated. In a recent study, Edelman et al. [12] examined the impact of two strategies that might counteract the effect of obesity on COC pharmacokinetics: elimination of the HFI or use of a higher-dose levonorgestrel (LNG)/EE regimen cyclically. In their study, obese women (body mass index [calculated as weight in kilograms divided by the square of height in meters] ≥30) used a 21/7-day LNG/EE (100 μg/20 μg) regimen (Aviane, Teva Pharmaceuticals, Petah Tikva, Israel) for two cycles and were then randomized to continuous LNG/EE (100 μg/20 μg) with no HFI or to higher-dose cyclic 21/7 LNG/EE (150 μg/30 μg; Portia, Barr Laboratories, Pomona, NY, USA). During the baseline cycle, the average time to reach the steady-state plasma LNG concentration was 12.3 days, and 45% of women had evidence of follicular activity [12]. After randomization, both continuous LNG/EE (100 μg/20 μg) and cyclic LNG/EE (150 μg/30 μg) reduced follicular activity as compared with the standard 21/7 LNG/EE (100 μg/20 μg) regimen. Only 9% of women in each group showed evidence of follicular activity [12]. Although the time to reach a steady LNG concentration was delayed for women using the higher-dose pill, the threshold level needed to inhibit the HPO axis was achieved earlier. Women using the lower-dose pill remained continuously at the steady-state level of plasma LNG.

These data indicate that ovarian suppression can be incomplete in regimens that include a 7-day HFI, particularly when very low estrogen doses are used. Incomplete ovarian suppression might have several important consequences, including an increase in follicular development, a heightened risk of escape ovulation, a potential reduction in contraceptive effectiveness, a potential increase in the risk of unscheduled bleeding, and an increase in the incidence and severity of hormone-withdrawal symptoms [1].

For example, Sulak et al. [2,17] have demonstrated that the adverse effects—e.g. headache, pelvic pain, bloating, breast tenderness, and use of pain medication—are significantly more frequent and more severe during the HFI than during the period of active COC use. These symptoms tend to increase during the last week of active pills and continue to increase during the HFI—a pattern that parallels the decrease in endogenous estrogen levels during the same period [18]. Therefore, modifying the HFI has the potential to reduce the frequency and severity of hormone-withdrawal symptoms related to COC use. Continuous dosing without an HFI has been found to reduce symptoms related to the menstrual cycle in users of a low-dose LNG/EE (100 μg/20 μg) pill [19].

Because ovarian activity and inadequate ovarian suppression occurring during the 7-day HFI have been associated with an increased risk of unscheduled bleeding in the following cycle [1], it is thought that increased ovarian suppression might reduce the risk of unscheduled bleeding and improve cycle control [20].

3.3. Alternatives to the traditional HFI

The limitations of the 7-day HFI—including inadequate ovarian suppression and the potential for hormone-withdrawal symptoms—reinforce the importance of alternative approaches to traditional COC regimens.

One option to improve ovarian suppression and reduce the incidence of hormone-withdrawal symptoms is to use extended or continuous regimens, which reduce the number of HFIs. In extended regimens, active COC pills are administered for longer than 28 days and the time between HFIs is extended. A frequently used extended regimen is the 84/7 regimen (84 active days, followed by 7 days of no treatment; Seasonale, Teva Women's Health, Sellersville, PA, USA) or

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