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Continuous oral contraception: changing times

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Oral contraceptives (OCs) remain the most common method of reversible contraception. Despite lowering of oestrogen and progestin content, the same basic design of 21 combination oestrogen plus progestin pills followed by a week of placebo pills has remained. Numerous studies have now documented that the 21/7 regimen needs to be modified. The 7-day hormone-free interval (HFI) in today's low-dose OCs is associated with reduced pituitary–ovarian suppression, allowing for ovarian follicular development, endogenous oestradiol production and possible ovarian cyst formation and ovulation. The 7-day HFI is also associated with hormone withdrawal symptoms that can lead to discontinuation and unintended pregnancy. Modifications in OC regimens are now appearing on the market secondary to the accumulated scientific data on the disadvantages of low-dose 21/7 pills. This article will review the data on problems with standard OC regimens and modifications that can improve the efficacy and side-effect profile.

Key words: extended regimen; oral contraceptive; menstrual symptoms; headache; endometriosis; hormone-free interval.

As oral contraceptives (OCs) have been available for over four decades, it is easy to forget that the introduction of reliable oral contraception – a widely available method that gave women control of their fertility – was revolutionary at the time. The decision to use a 28-day pill regimen was not a response to a physiological need for 13 cycles per year, but was dictated by the social norms and pregnancy testing technology of the day. At a time when pregnancy testing was neither easy to perform nor highly sensitive, the 7-day hormone-free interval (HFI) provided a monthly reassurance to the OC user that she was not pregnant by inducing hormone withdrawal bleeding. Over the ensuing years, numerous improvements in oral contraception have taken place, such as

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lowering of oestrogen content to minimize complications, confirmation of the efficacy of low-dose pills, and introduction of new progestins. These changes came about due to clinical trial evidence and scientific assessments of OC regimens. Most recently, the focus of OC research has shifted towards alteration or elimination of the 7-day HFI with the goal of reducing withdrawal bleeding, minimizing hormone withdrawal symptoms and maximizing ovarian follicular suppression.

DRAWBACKS OF THE 21/7 REGIMEN

While 21/7 OCs have been the mainstay over the 45-year history of the pill, reductions in dosage have led to a need to redesign the standard regimen with a focus on modifications in the 7-day HFI.

Lack of pituitary–ovarian suppression

Today's conventional 28-day (21 days active/7 days placebo) low-dose OCs [$\leq$35 μg ethinyl oestradiol (EO)] fail to induce complete ovarian suppression.[1,2] The goal of OC therapy is prevention of pregnancy by suppression of ovarian follicular development and ovulation. Follicular development during the HFI of traditional 21/7-day OC regimens resembles that usually seen during the early follicular phase of the natural menstrual cycle.[3–5] Several studies have evaluated follicular development during the HFI of OC regimens with variable doses of oestrogen and progestin, length of HFI and use of low-dose EO during the HFI.[6–11] Oestradiol levels begin to rise at the end of the 7-day HFI, peak in the first half of the next OC cycle, then decline during the last week of active pills.[11–13] Spona et al were the first to report greater suppression of ovarian activity with a shortened HFI.[13] By increasing the number of active pills from 21 to 23 per cycle and decreasing the HFI from 7 to 5 days, there was lower residual ovarian activity and endogenous 17β-oestradiol. The study also showed that 17β-oestradiol levels begin to rise during the HFI, with the rise earlier and greater in women assigned to the 21-day regimen.

Recently, Baerwald et al evaluated the effects of initiation of OC therapy at defined stages of follicular development.[8] Women were randomized to initiate OC (30 μg EO + 150 μg desogestrel) use when follicle diameters of 10, 14 or 18 mm were detected after menses. The number of developing follicles, incidence of ovulation and peak plasma levels of oestradiol and luteinizing hormone (LH) correlated directly with size of follicles at the initiation of OC therapy. Ovulation occurred in both the 14-mm (4/14 follicles; 29%) and 18-mm (14/15; 93%) baseline follicle size groups. The results of this study support the notion that women initiating OC therapy at later stages of the menstrual cycle may be at increased risk of ovulation. This concept may be extrapolated to a potential for increased risk of ovulation when the HFI extends beyond 7 days.

The effects of manipulation of the 7-day HFI on follicular development have been measured in several controlled studies.[6,10,11] In the first, women were randomized to one of three OC regimens containing 20 μg EO with a 7-day HFI, a 2-day HFI with 5 days of low-dose EO or no HFI (28-day continuous regimen).[6] Total follicle count and follicle index were assessed from the first day of the second cycle (overall day 29). A significant difference in the total follicle count among the three groups ($P = 0.005$) was reported. Women who continued combined active therapy during