
Evolving Strategies in the Dosing of Oral Contraceptives

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Oral contraceptives are used by millions of women worldwide, and are the most common form of birth control chosen by Canadian women.¹ In Canada, 18% of women aged 15-49 use the combined oral contraceptive (COC), and of Canadian women who use contraception, 32% choose COCs as their primary form of birth control.^{2,3}

Since the introduction of the first COC in 1960, COCs have undergone many modifications. Most notably, the amount of estrogen has declined steadily over the years, with today's low-dose COCs containing $\leq 35\mu\text{g}$ ethinyl estradiol (EE). In addition, new progestins—with varying degrees of progestational potency, as well as estrogenic, anti-estrogenic, or androgenic activity—have emerged over the past 50 years. Depending on the COC, the amount of estrogen and/or progestin may be varied weekly.¹

In Canada, one aspect of the COC that has undergone limited modification is the way in which COCs are dosed. COCs were originally designed to be taken for 21 days, followed by a seven-day hormone-free interval (HFI). While the reasons for choosing an HFI of seven days may have been more happenstance than scientific dictum, the 21/7 dosing regimen has become the standard dosing regimen for OCs.⁴ Over time, women have come to take the 21/7 dosing regimen for granted.

Suppression of menstruation through elimination of the HFI is one modification to the dosing regimen that has been used in the medical community for many years, and is gaining acceptance among Canadian women. The Society of Obstetricians and Gynaecologists of Canada (SOGC) recognizes the use of continuous and extended combined hormonal products in women who are comfortable eliminating their withdrawal period.⁴ While a dedicated, extended COC product is available in Canada, all currently available EE contraceptives (oral [monophasic or multiphasic], transdermal, vaginal) $< 50\mu\text{g}$ can be used in a continuous and/or extended regimen.⁴ The majority of Canadian women taking COCs, however, still follow the conventional 21/7 dosing regimen.

RATIONALE FOR MODIFYING THE 7-DAY HORMONE-FREE INTERVAL

Risk of Escape Ovulation

The purpose of the COC is to inhibit ovulation, primarily through suppression of gonadotropin secretion.¹ With perfect use, the COC is 99.9% effective in preventing pregnancy, although a 3-8% failure rate exists with typical use.⁵⁻⁷

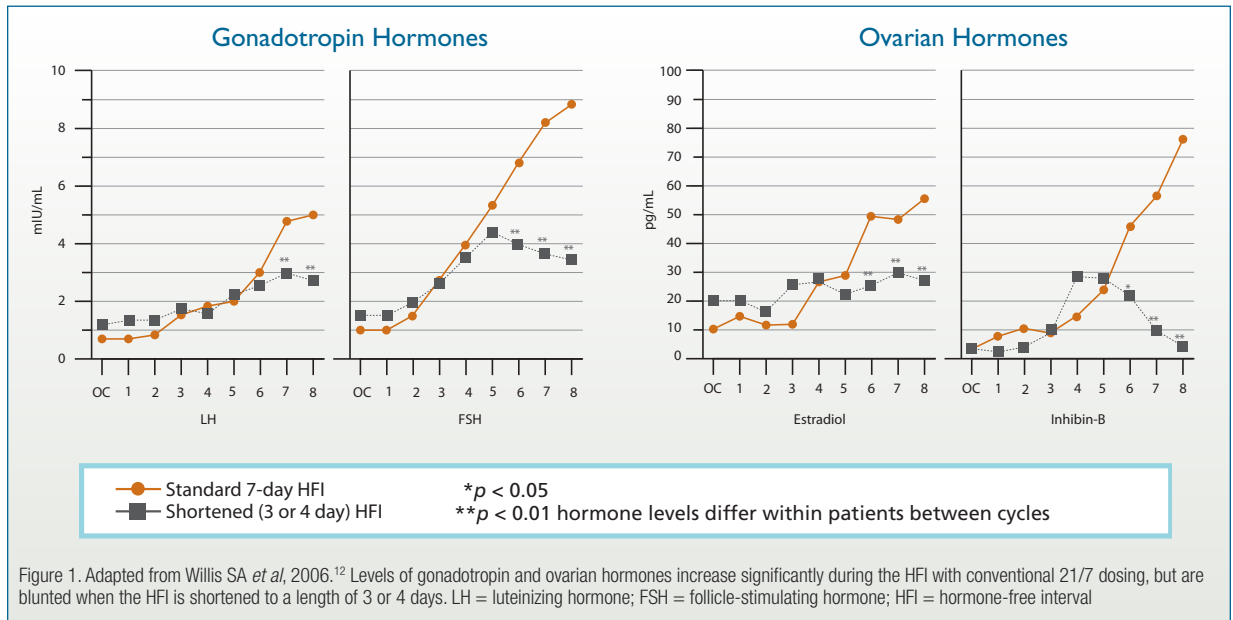


Figure 1. Adapted from Willis SA *et al*, 2006.¹² Levels of gonadotropin and ovarian hormones increase significantly during the HFI with conventional 21/7 dosing, but are blunted when the HFI is shortened to a length of 3 or 4 days. LH = luteinizing hormone; FSH = follicle-stimulating hormone; HFI = hormone-free interval

In the past, oral contraceptives contained higher doses of estrogen and progestin. These higher-dose pills required five days for serum hormone levels to drop low enough to allow endometrium sloughing and permit a withdrawal bleed.⁵ With today's lower-dose formulations, endometrial sloughing begins within two days of the last active pill.⁸ Subsequently, endogenous hormone levels, which are usually suppressed by exogenous hormones, begin to rise throughout the HFI.

Ovarian follicular recruitment with low-dose formulations therefore begins much earlier in the HFI, making escape ovulation more likely.⁸ Risk of escape ovulation is further increased if a woman misses pills at the end of her pack or the beginning of her next pack, as this further extends the HFI.⁸ Studies have confirmed an incomplete suppression of ovarian function in COC users, allowing follicular growth and subsequent endogenous hormone production.⁹⁻¹²

In a three-month prospective study by Willis SA *et al*, 12 current OC users were given a monophasic OC containing 30 µg of EE and 3 mg of drospirenone.¹² Participants completed one baseline 21/7 cycle of the study OC, followed by two successive cycles with a shortened HFI of three (n=6) or four (n=6) days. All subjects resumed active pills following the shortened HFI. Nine daily blood samples were obtained for the measurement of follicle-stimulating hormone (FSH), luteinizing hormone (LH),

estradiol and inhibin-B, beginning with the last active pill (Day 21) of each cycle and continuing through the HFI into the next cycle. Analysis of variance was used to compare hormones for nine days bracketing the standard seven-day HFI and to compare the seven-day HFI and the subsequent shortened HFI within individuals.

Activation of the pituitary-ovarian axis was found to occur during the seven-day HFI.¹² During the seven hormone-free days, levels of LH, FSH, estradiol and inhibin-B increased significantly (Figure 1). FSH levels show significant increases by Day 4 of the HFI, allowing subsequent follicular recruitment and estradiol production. These findings indicate that there is a potential for ovulation during the HFI, and may explain why some women correctly taking a COC still develop ovarian cysts.

Hormonal Fluctuations

As much as 90% of women of reproductive age experience some form of premenstrual symptoms, also known as premenstrual molimina.^{13,14} In more than 30% of these women, the symptoms are severe enough to be classified as premenstrual syndrome (PMS); and up to 8% of women experience the most severe form of premenstrual symptoms, known as premenstrual dysphoric disorder (PMDD).¹⁵⁻¹⁹ While the exact cause of premenstrual symptoms is unknown, fluctuating hormones are thought to be one possible trigger.

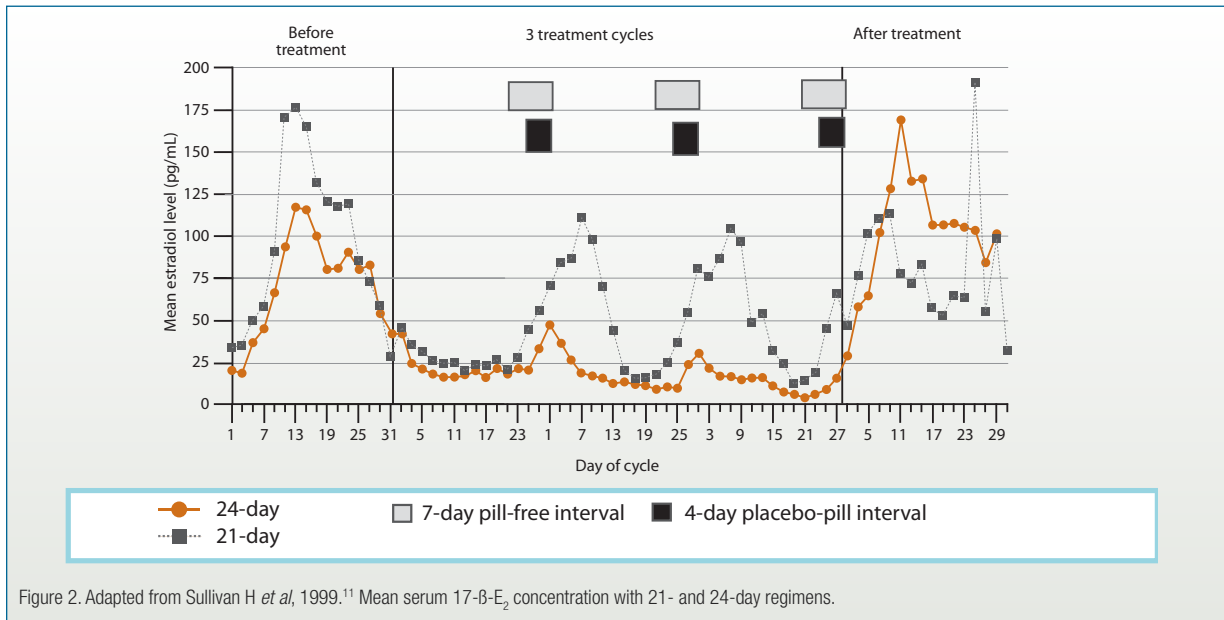


Figure 2. Adapted from Sullivan H *et al*, 1999.¹¹ Mean serum 17-β-E₂ concentration with 21- and 24-day regimens.

COCs regulate the menstrual cycle and help to stabilize hormonal fluctuations. They have been shown to have a positive effect on certain physical premenstrual and menstrual symptoms, including dysmenorrhea, acne and heavy flow.¹

COCs containing the progestin drospirenone (a spironolactone analogue) have additionally been shown to relieve premenstrual and menstrual symptoms of bloating and swelling.²⁰ Most importantly, they are the only COCs proven to relieve certain emotional premenstrual symptoms by improving mood, appetite and food cravings.²¹⁻²⁷ This hormone combination has been shown to be efficacious to alleviate physical and emotional symptoms, even among those who present with the most severe/impairing form of PMS/PMDD.^{28,29}

Although COCs help stabilize hormone levels, hormonal fluctuations can still occur during the HFI. Two open-label studies were conducted in healthy women taking a COC containing 60 µg of gestodene and 15 µg of EE for three treatment cycles.¹¹ Differences in ovulation inhibition and ovarian activity was assessed in subjects following a 21-day regimen versus those following a 24-day regimen.¹¹ Interestingly, while mean serum 17-β-E₂ levels rose during the HFI in both groups, a much greater increase was observed in the 21/7 group (Figure 2).¹¹ Serum 17-β-E₂ levels remained at < 50 pg/mL during treatment in patients following the 24/4 dosing regimen, but were increased to > 100 pg/mL in women

following conventional 21/7 dosing (Figure 2).¹¹

Moreover, in a 2000 study by Sulak *et al*, it was demonstrated that up to 70% of women may experience hormone-withdrawal symptoms during the HFI, including nausea, vomiting, breast tenderness, bloating, swelling, headaches, unscheduled bleeding/spotting, and mood changes (Table 1).^{4,30} Together these studies indicate that hormonal fluctuations occur during the HFI, and may result in hormone-withdrawal symptoms in OC users.

Elimination of the Hormone-Free Interval

Suppression of menstruation through elimination of the HFI has been used in the medical community for many years, and is gaining acceptance among many women.⁴

A number of advantages have been associated with eliminating the HFI, including: decreased incidence of pelvic pain, headaches, bloating/swelling and breast tenderness; improved control over symptoms of endometriosis and polycystic ovary syndrome (*i.e.*, acne, seborrhea and hirsutism); and greater convenience due to fewer withdrawal bleeds per year.^{1,4}

Extended and continuous dosing regimens, however, are not without some disadvantages. Most notably, these regimens have been associated with an increased incidence of unscheduled bleeding and spotting.⁴ Moreover, a number of women are not comfortable eliminating menstruation completely, for personal, social, cultural or religious reasons.⁴

TABLE 1 Hormone Withdrawal Symptoms in OC Users

Symptoms	Hormone Treatment (21 days)	Hormone-Free Interval (7 days)	P-value
Pelvic pain	21%	70%	< 0.001
Headaches	53%	70%	< 0.001
Breast tenderness	19%	58%	< 0.001
Bloating/swelling	16%	38%	< 0.001
Use of pain medication	43%	69%	< 0.001

Adapted from Sulak P *et al*, 2000.³⁰

ADVANTAGES OF SHORTENING THE HORMONE-FREE INTERVAL

Reduce the Risk of Escape Ovulation

As discussed previously, significant activation of the pituitary-ovarian axis occurs during the HFI, allowing at least some ovarian follicular growth that could lead to ovulation (Figure 1).¹² When the HFI was shortened from the standard seven days to a length of three or four days, increases in the gonadotropin and ovarian hormones were blunted (Figure 1).¹² These findings suggest that a 24/4 or 25/3 dosing regimen would provide greater pituitary-ovarian inhibition, resulting in a reduced risk of ovulation and cyst formation, as well as the potential for a lower incidence of common hormone-withdrawal symptoms compared to standard 21/7 dosing.¹²

Shortening the HFI is therefore an innovative solution to help reduce the risk of ovulation during the HFI with today's low-dose OCs. This was further demonstrated in a recent double-blind, randomized study by Klipping *et al*, where ovarian activity was measured in women taking a 20 µg EE/3.0 mg drospirenone OC in either the conventional 21/7 dosing regimen (n=52) or a 24/4 dosing regimen (n=52) for three treatment cycles (Figure 3).³¹ Ovarian activity was classified according to the Hoogland scoring system, which combines data on follicular activity obtained from transvaginal ultrasonography and serum hormone determinations, including progesterone and endogenous estrogen (E₂) measures. Primary efficacy variables in this study were the Hoogland scores in Cycle 2 and Cycle 3.

In Cycle 2 of this study, women in the 24/4 group had greater suppression of ovarian activity compared to women in the 21/7 group, with a more consistent suppression of endogenous E₂ and endogenous hor-

monal fluctuations.³¹ Moreover, in the conventional 21/7 group, one woman out of 52 ovulated and another had a luteinized unruptured follicle; neither of these events occurred in the 24/4 group (Figure 4).

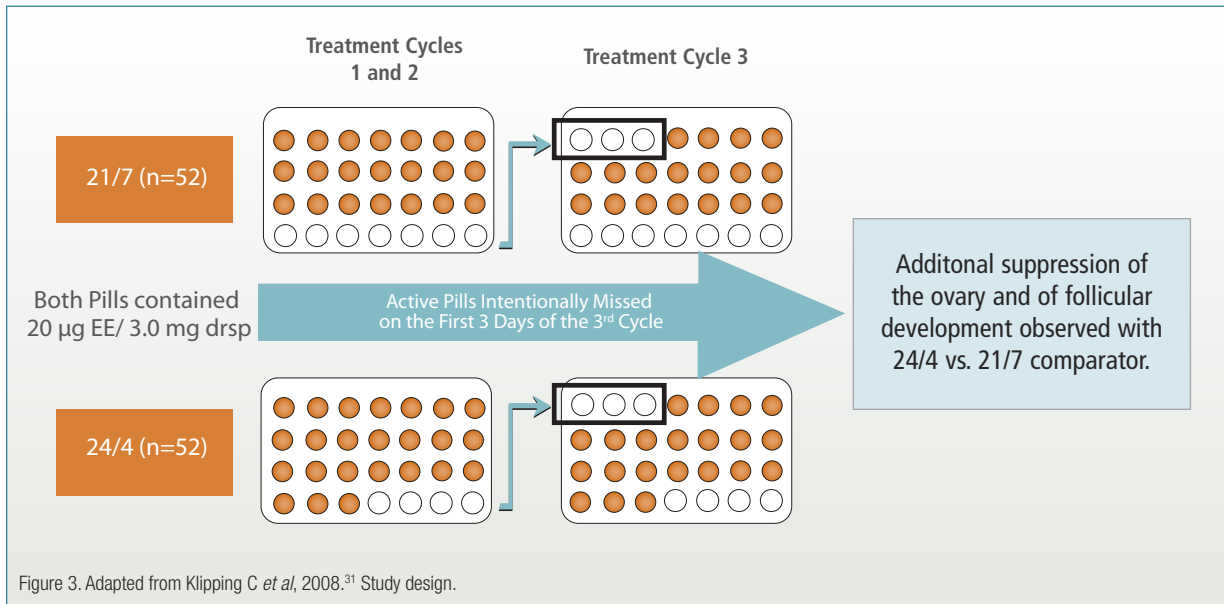
In Cycle 3, women in both groups were instructed to intentionally miss the first three active pills at the beginning of the cycle (Figure 3).³¹ Again, women in the 24/4 group had less ovarian activity than women in the 21/7 group, with only one woman out of 52 ovulating compared to four out of 52 in the 21/7 group (Figure 4). Women in the 24/4 group also had less follicular development following intentional dosing error compared to women in the 21/7 group.

Missed pills are a reality for OC users. In a prospective U.S. study, it was determined that as many as 81% of women missed at least one pill over a three-month period.³² Surprisingly, as many as 30-51% of women missed at least three pills in three months³², with most women citing "no new pack" as their reason for missing consecutive pills.³³ These findings suggest that a significant number of women extend the HFI beyond the recommended seven-day period.

Since the pituitary-ovarian axis is significantly activated during the HFI, if a patient misses any pills—thereby extending the HFI—the risk of escape ovulation, and possible pregnancy, becomes significant.¹² In clinical practice, shortening the HFI may therefore increase the contraceptive safety margin when pills are omitted or missed compared to conventional 21/7 dosing.³¹

Minimize Hormonal Fluctuations

As previously discussed, hormonal fluctuations occur during the HFI (Figure 2).¹¹ With conventional 21/7 dosing, up to 70% of women may experience hormone-withdrawal symptoms during the HFI, such as nausea, vomiting, breast tenderness, bloating,



swelling, headaches, unscheduled bleeding and spotting, and mood changes (Table 1).^{4,30}

Reducing the HFI to three or four days has been shown to improve quality of life in 82% of subjects, mainly by improving their menstrual-associated symptoms.⁴ Moreover, as discussed previously, the 24/4 regimen was associated with a more consistent suppression of endogenous E₂ and endogenous hormonal fluctuations.^{11,31} Together, these findings suggest that 24/4 dosing may reduce hormonal fluctuations, reducing hormone-withdrawal symptoms and improving quality of life.

24/4: A New COC Dosing Regimen With a Shortened Hormone-Free Interval

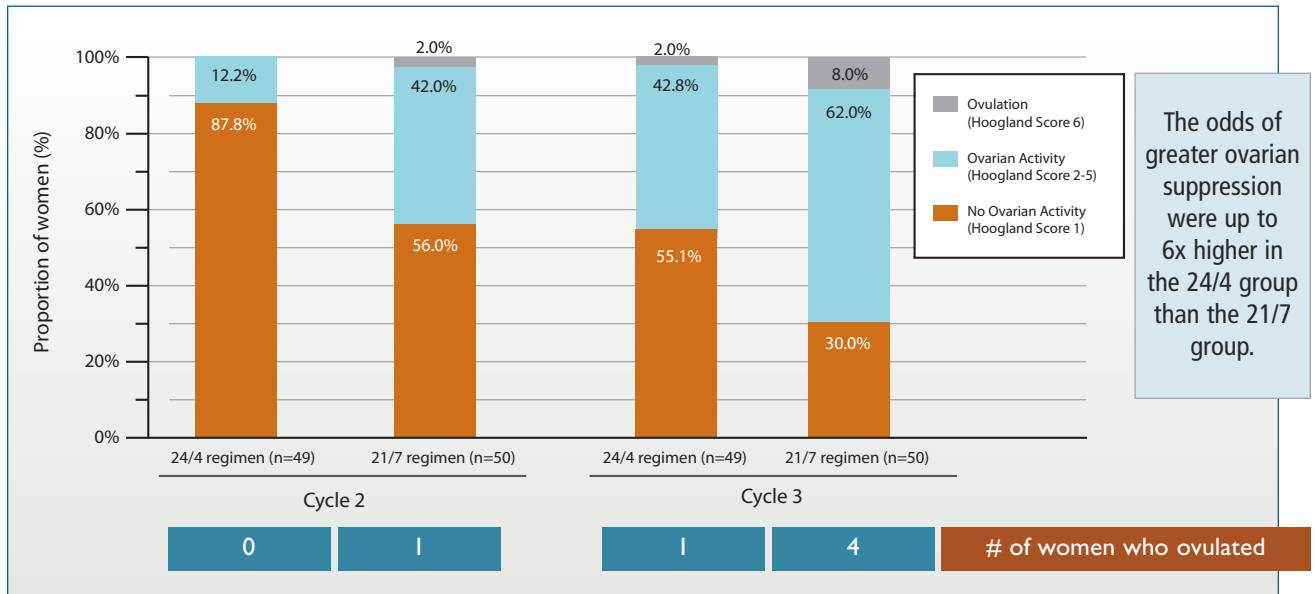
COCs with a dosing regimen of 24 active pills, followed by four inactive pills, are currently available in many countries, including the U.S., Europe, Australia, Asia-Pacific and Latin America. A new COC with this dosing regimen has recently been approved and launched in Canada.

This new dosing regimen—known as 24/4—offers many advantages over the conventional 21/7 dosing regimen, including greater suppression of ovarian activity and follicular development, with decreased risk of ovulation.^{12,31} It also provides users with a reduced potential for the development of ovarian cysts and allows an increased contraceptive safety margin if pills are missed.^{12,31} Furthermore, 24/4 dosing prevents hormonal fluctuations, helping to reduce the hormone-

withdrawal symptoms experienced by most pill-users during the HFI, and to improve quality of life.^{4,30,31} The 24/4 dosing regimen is the only available cyclical dosing regimen to offer these benefits, and is of particular interest to women who, for personal, cultural or religious reasons, wish to have a monthly withdrawal bleed.

Conclusion

Since the introduction of the Pill in 1960, the formulation of the COC has continuously evolved, giving us today's modern low-dose ($\leq 35 \mu\text{g}$ EE) COCs.¹ The conventional 21/7 OC dosing regimen, however, has been used for almost 50 years, and is still the accepted dosing regimen for the majority of Canadian OC users.⁴ With today's low-dose formulations, endogenous hormone levels, which are usually suppressed by exogenous hormones, begin to rise throughout the typical seven-day HFI.⁸ These hormone changes increase the risk of escape ovulation and may lead to hormone-withdrawal symptoms, which affect as many as 70% of pill users.^{4,8,30} Therefore, in an effort to adapt to today's low-dose formulations, we suggest modifying the length of the HFI. While eliminating the HFI offers many advantages to users, many women are not comfortable eliminating menstruation completely, for personal, cultural or religious reasons.⁴ As previously discussed, shortening the HFI using a 24/4 dosing regimen would therefore offer women the aforementioned benefits associated with modifying the HFI, without elimination of menstruation.



The odds of greater ovarian suppression were up to 6x higher in the 24/4 group than the 21/7 group.

Figure 4. Adapted from Klipping C *et al*, 2008.³¹ Randomized, double-blind, parallel group, comparison study conducted in healthy women (18-35 years) who ovulated or had a follicular diameter of ≥ 15 mm on or before Day 23 during a pretreatment cycle. Participants underwent 3 treatment cycles and blood samples were obtained every 3 days to measure estradiol levels. Ovarian activity was classified using the Hoogland scale during pretreatment and during Cycles 2 and 3. Active pills of each regimen were intentionally missed on the first 3 days of Cycle 3.

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