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Review Article

Ultra-low-dose oral contraceptive pill: a new approach to a conventional requirement

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ABSTRACT

Combined oral contraceptives (COCs) offer a convenient, safe, effective, and reversible method of contraception. However, their use is limited by side effects. Several strategies have been suggested to make COC use more acceptable among women. Reduction in the dose of estrogen is a commonly accepted approach to reduce the side effects of COC. Use of newer generation of progestins, such as gestodene, reduces the androgenic side effects generally associated with progestogens. Furthermore, reduction in hormone-free interval, as a 24/4 regimen, can reduce the risk of escape ovulation (hence preventing contraceptive failure) and breakthrough bleeding. It also reduces hormonal fluctuations, thereby reducing the withdrawal symptoms. A COC with gestodene 60 µg and ethinylestradiol (EE) 15 µg offers the lowest hormonal dose in 24/4 treatment regimen. This regimen has been shown to offer good contraceptive efficacy and cycle control. With the progress of treatment cycles, the incidence of breakthrough bleeding reduces. Gestodene/EE low dose 24/4 regimen was associated with lower incidence of estrogen-related adverse events, such as headache, breast tenderness, and nausea. Furthermore, COCs containing low dose of estrogen have not been associated with any adverse effect on haemostasis in healthy women. Ultra-low-dose COCs can be considered in women who are at risk of developing estrogen-related side effects.

Keywords: Combined oral contraceptive, Gestodene, Ethinylestradiol, Ultra-low dose contraceptive, 24/4 regimen

INTRODUCTION

The era of oral contraception began in 1960s, with the availability of the first COC (comprising progestin and estrogen), commonly known as the “pill.” The COC inhibits ovulation and implantation, thereby preventing pregnancy. Progestins prevent ovulation, mediated by negative feedback mechanism resulting in a decrease in luteinizing hormone (LH). Progestin also reduces cervical mucus receptivity of the sperm and endometrial thickness. Estrogen contributes to the antioviulatory mechanism of COCs by suppressing both follicle - stimulating hormones (FSH) and LH. It also helps in stabilizing the endometrium, thus providing better cycle control.¹

Ever since its availability, the COC has been used by millions of women across the world as a convenient, safe, effective, and reversible method of contraception.¹Recent estimates suggest that 9% of women in reproductive age across the world use the pill. It is the most common method of contraception in industrialised countries and the third most common method of contraception in developing countries.²

The patterns of contraceptive use have been evaluated in the National Family Health Survey-3 (NFHS-3). Despite 85% of surveyed women agreeing to know about the pill, the use of the pill was low; only 3.1% of married women use the pill.³The principal reason given by COC users for discontinuing the method is side effects.⁴

Milestones in the Evolution of COCs

Due to the higher concentrations of estrogens and progestins, early COCs were often associated with intolerable side effects, including irregular bleeding, nausea, headache, weight gain, and episodes of venous thromboembolism.² Discontinuation of contraceptive methods remains a major challenge for family planning program managers. According to the NFHS-3 data, despite lower failure rates (3%), discontinuation rate for pills was 49%; the most common reason for discontinuation was the concern about side effects or health problems.³

Accordingly, attempts have been made to reduce the side effects of COCs, which involved modifications of hormone doses and types, dosage regimens, and administration schedules. The evolutionary steps undergone by COCs over the past half century have been summarised in Table 1.¹

Reduction in the dose of estrogens has been a significant modification in the evolution of COCs. This was done with the intention of improving the safety and tolerability profile of COCs without compromising its effectiveness.¹ While earlier generations of COCs have up to 150 µg of estrogen, the modern pills have 20µg (low-dose COC) or 15µg (ultra-low-dose COC) of estrogen. Ultra-low-dose COCs have the lowest dose of estrogen (15µg) and have been approved in Eastern countries and in India.⁵ However, the low doses of estrogen used in modern low- and ultra-low-dose COCs are inadequate to produce a consistent antiovarulatory effect. Thus, the focus has shifted to the progestin component, which contributes to the majority of antiovarulatory effects of COCs.⁶

PROGESTINS

Based on the time of introduction, the progestins have been classified into four generations, as shown in Table 2.⁷

Progesterone is the only natural type of progesterone. A broad spectrum of synthetic progestins have been prepared from different parent compounds.⁸ Depending on its chemical structure, the biological activity of a progestogen changes considerably.⁸

It has been known that effects of progestins are not only dependent on its interaction with progesterone receptors but also with other steroid hormone receptors, including androgen receptors, estrogen receptors, glucocorticoid receptors, or mineralocorticoid receptors. While all progestins bind to progesterone receptors, each progestin has a distinctive profile of affinity for other receptors, which might not be shared even among the other members of the same class.⁶ With such varied affinities, it is now possible to select a progestin to suit an individual patient (Table 3).²

Levonorgestrel has no estrogenic but strong anti-estrogenic activity, along with no mineralocorticoid and glucocorticoid activities. Drospirenone has strong progestogenic activity, along with anti-aldosterone activity and natriuretic effect. It also has strong antiminerocorticoid activity.²

Since the earlier progestins were specifically designed for their contraceptive use, they primarily had antigonadotropic activity. Later, the focus was shifted toward creating an "ideal" progestin, with potent progestational and antiestrogenic actions on the endometrium, a strong antigonadotropic effect, but without any androgenic or glucocorticoid effects. This was expected to offer the benefits of progesterone without undesirable effects, such as causing acne, a decrease in high-density lipoprotein cholesterol, bloating, and water retention.⁶

A focus on Gestodene

In order to minimise the androgenic effects, progestins such as gestodene, desogestrel, and norgestimate were introduced. Gestodene, a 19-nortestosterone derivative, is a widely-used progestin. Structurally, gestodene has an additional double bond between C-15 and C-16 in the D-ring to levonorgestrel. This double bond leads to a conformational change in the 18-ethyl group, affecting the pharmacokinetics of the molecule. The androgenic affinity of gestodene is twice as that of levonorgestrel; however, the progestational to androgenic effect ratio of gestodene remains higher than that of levonorgestrel. Gestodene, unlike desogestrel and norgestimate, is not a prodrug. Furthermore, with a higher affinity for sex-hormone binding globulin, gestodene has a lower metabolic clearance rate and a greater concentration in the circulation. This aspect may be particularly beneficial in case of missed pills. Furthermore, the longer half-life and an alternative regimen (24/4 regimen, which will be discussed later) contribute to the reduction in failure rate of COCs.⁹

A new approach to reducing hormone free interval: The 24/4 regimen

The classical 21/7 regimen

Since the time of availability, the COCs have been offered as a 21/7 regimen, which involves 21 days of active treatment, followed by a 7-day hormone-free interval (HFI), when a withdrawal bleed usually occurs. Classically, this regimen was used in an attempt to mimic the natural monthly menstrual cycle in women, improving the general acceptance. This also reduced the concerns of not having bled on a monthly basis and also provided an assurance of not being pregnant.^{10,11}

However, it has been suggested that the 21/7 regimen has its own sets of concerns.¹¹ Evidence suggests that 21/7 COC regimens might not adequately suppress ovarian

activity and follicular development.¹⁰ With the current low-dose pills, endometrial sloughing begins within 2 days of the last active pill. The ovarian follicular recruitment begins much earlier in HFI, making escape ovulation more likely.¹²The problem is substantial with a missed or late start of the next COC pill cycle, consequently resulting in contraceptive failure.¹¹

Another major problem is that the pill-free interval allows recurrence of withdrawal symptoms, such as headache, acne, and premenstrual symptoms, which are otherwise controlled by active pills.¹¹

Table 1: Evolution of COC.¹

Decades	Milestones
1960s	Introduction of first oral contraceptives in Europe and Australia
	In Europe, pill was only recommended for regulating menstrual disorders and in married women.
1970s	Introduction of ‘mini pill’ (progestin only pill)
	Publication of initial reports of use of COC and thromboembolic events
1980s	Introduction of biphasic and triphasic pills
	Reduction in use of high dose estrogen containing pills
	Recognition of other health benefits and fact that health benefits of COC outweigh the possible health risks in nonsmoking women over 40 years
1990s	Introduction of low dose COCs
2000s	Introduction of extended and continuous regimen COCs
	Development and introduction of newer progestins
	Introduction of non-oral combined hormonal contraceptives preparations
2010s	Use of natural estrogens in COC regimens
	Further investigations on newer progestins
	Investigation on genetic and proteomic targets for contraception

Table 2: Classification of progestins on the basis of time of introduction.⁷

First generation	Second generation	Third generation	Newer progestins
Pregnanes			19 nor-progesterones
Chlormadinone acetate			Promegestone
Cyproterone acetate			Trimegestone
Megestrol acetate			Demegestone
Estranes			Nesterone
Noerethindrone	DI-norgestrel	Desogestrel	Nomegestrol acetate
norethindrone acetate	Levonorgestrel	Norgestimate	Gonanes
Ethinodiol diacetate		Gestodene	Norelgestromine
Lynestrinol			Etonogestrel
Norethynodrel			Estranes
			Dienogest
			(non-ethylated)
			Spirolactone derivative
			Drospirenone

The 24/4 approach

In order to avoid the limitations of the 7-day HFI, alternative approaches to the traditional 21/7 regimen have been explored. One of these options has been to reduce the HFI with extended or continuous regimens. A 24/4 regimen, involving a dosing regimen of 24 days of active treatment followed by four days of inactive pills,

was introduced as a means to reduce the HFI.¹¹ There are several advantages of shortening the HFI, some of which are discussed below:

Reduction in risk of escape ovulation

During the HFI, there is significant activation of the pituitary-ovarian axis, allowing at least some ovarian

follicular growth that could lead to ovulation. Missing the pills will further extend the HFI, posing higher risk of escape ovulation and possible pregnancy.¹² A study conducted by Wills *et al.* has shown that a reduction in HFI from 7 to 4 or 3 days leads to lower peaks in the gonadotropin and ovarian hormones (Figure 1).¹³ The

24/4 dosing regimen offers greater pituitary-ovarian inhibition, and thus, a lower risk of ovulation and cyst formation, as well as the potential for lower incidence of common hormone-withdrawal symptoms compared to standard 21/7 dosing.¹²

Table 3: Effects of different progestins²

	Anti-estrogenic activity	Androgenic activity	Anti-androgenic activity	Anti-mineralocorticoid activity
Progesteron	+	-	+	+
Levonorgestrel	+	+	-	-
Gestodene	+	+	-	+
Desogestrel	+	+	+	-
Cyproterone	+	-	+	+
Desonorgestrel	+	-	+	-

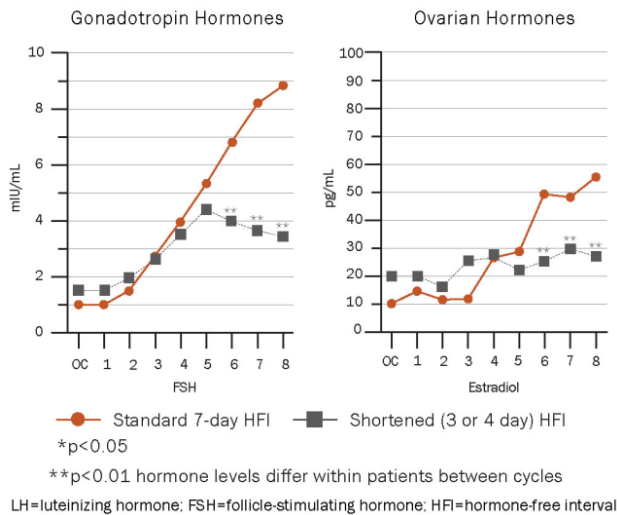


Figure 1: Levels of gonadotropin and ovarian hormones increase significantly during the HFI with conventional 21/7 dosing, but are blunted when the HFI is shortened to a length of 3 or 4 days.

A randomised, double-blind study (Klippling *et al.*) compared ovarian activity with the use of COC containing EE/drospirenone (20 µg/3.0 mg) in 21/7 and 24/4 regimens for three treatment cycles. It was reported that by the second cycle of treatment, ovulation and luteinized unruptured follicle had occurred in 1 woman each in the conventional 21/7 group and none in the 24/4 regimen. Furthermore, with the intentional missing of three pills at the beginning of cycle 3, the ovarian activity was less in the 24/4 regimen (one woman of 52 women who ovulated) compared with the 21/7 regimen (four women of 52 women who ovulated).¹⁴ It has been reported that with 21/7 regimen, the follicular growth during HFI may become suitable for preferential growth and eventually ovulation. Prolongation of HFI, due to

missed pills, may further increase the risk of follicular maturation and escape ovulation.¹⁵ Clinically, compared with 21/7 regimen, shortening the HFI with 24/4 regimen may increase the contraceptive safety margin when pills are omitted or missed.¹²

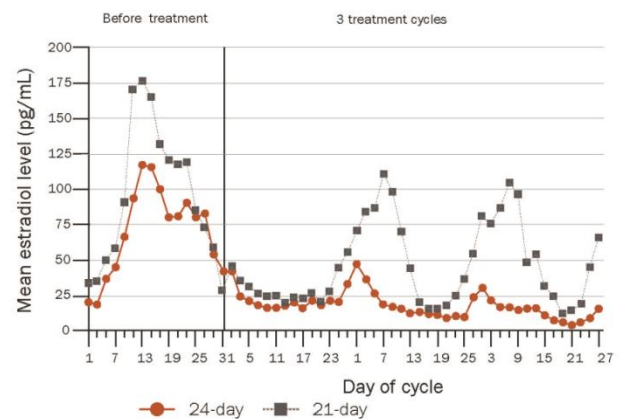


Figure 2: Mean serum 17-beta E2 concentration with 21- and 24- regimens.

Minimise hormonal fluctuations

Fluctuating hormone levels have been considered to contribute toward premenstrual symptoms that commonly occur during HFI.¹² It has been shown that with use of COC containing gestodene/EE (60/15µg) over three treatment cycles, there were lower fluctuations in 17-β-E2 levels with 24/4 regimen, compared with 21/7 regimen (Figure 2).¹⁶

It has been reported that up to 70% of women on 21/7 COC regimen experienced hormone-withdrawal symptoms during the HFI, such as nausea, vomiting, breast tenderness, bloating, swelling, headaches,

unscheduled bleeding and spotting, and mood changes. Reducing the HFI was shown to improve the quality of life in 82% of women.¹⁷

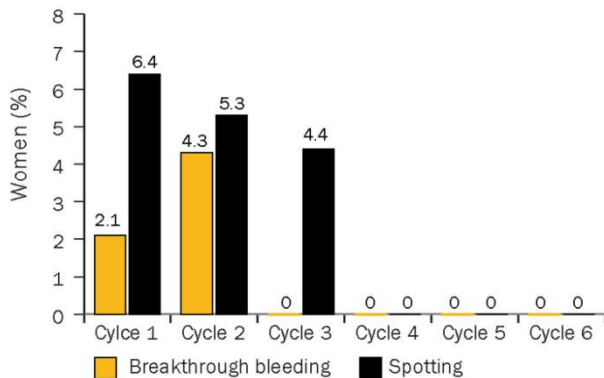


Figure 3: Percentage of breakthrough bleeding and spotting in each cycle.

Highlights of the 24/4 regimen

The highlights of the 24/7 COC regimen are summarised below:¹²

1. Greater suppression of ovarian activity and follicular development with decreased risk of ovulation
2. Allows an increased contraceptive safety margin if pills are missed
3. Prevents hormonal fluctuations that help in reducing the hormone withdrawal symptoms during the HFI and improving quality of life
4. Beneficial in case of women who, for personal, cultural, or religious reasons, wish to have a monthly withdrawal bleed

The Ultra-low-dose COC: Clinical evidence

A COC with gestodene 60µg and EE 15µg offers the lowest hormonal dose in 24/4 treatment regimen. The clinical evidences regarding its efficacy and safety are discussed below.

Contraceptive efficacy and cycle control

An open-label, multicenter study evaluated the contraceptive efficacy, cycle control, and safety of 24/4 regimen of gestodene 60 µg and EE 15µg. A total of 1496 women were exposed to at least one tablet of COC and were included in the intention-to-treat population in this study. Three pregnancies were reported during 18,194 treatment cycles among 1424 women, with a pearl index of 0.21. 136 women (9%) did not take three or more active pills in at least one cycle. Furthermore, in 1837 (10%) cycles of treatment, at least one treatment pill was missed by the participant. Overall, 72% of the cycles were normal, with proportion of normal cycles being 57% at treatment cycle 1 and improving to 73% by treatment cycle 19. A pattern toward reduction in

incidence of breakthrough bleeding was noted with advancing treatment cycles. In 7% of the cycles, there was no withdrawal bleeding.¹⁸

Jaithithivit *et al.* conducted an open-label, non-comparative study to determine the cycle control, safety, and acceptability of six treatment cycles of 24/4 regimen of gestodene/EE (60/15 µg) in 94 women. No pregnancy was reported during this study. The overall incidence of normal cycle was 86%. Incidences of breakthrough bleeding and spotting were 2.1% and 6.4%, respectively, in the first cycle, which then declined and were completely eliminated after the third cycle (Figure 3). Amenorrhea was noted in 1%-4% of women in the initial four cycles but was not noted in the later cycles. Furthermore, the length of withdrawal bleeding duration was also reduced from 4.5 days in the first cycle to 3.9 days in the sixth cycle. At the end of the study, 93.6% of women were satisfied or very satisfied physically. Furthermore, 95.8% of women reported emotional satisfaction or high satisfaction. Given a choice, 91.5% of women wished to continue the regimen in future.¹⁹

Another prospective, open-label, multicenter study conducted by Barbosa *et al.* evaluated the efficacy of gestodene/EE 24/4 regimen for 6 months. Only one undesired pregnancy was reported while on treatment. Compared with baseline, there was a reduction in the mean cycle length. At the end of the sixth cycle, 49% of women had experienced a reduction in bleeding intensity compared with baseline. The incidence of breakthrough bleeding declined with the treatment cycles.²⁰

Safety

The use of lower hormonal doses in COC has the potential to reduce common side effects associated with oral contraceptive use, such as nausea and breast tenderness. Gestodene/EE low dose 24/4 regimen was associated with lower incidence of estrogen-related adverse events, such as headache, breast tenderness, and nausea.¹⁸

In the study by Jaithithivit *et al.*, only minimal side effects were reported. Headache was the most commonly reported side effect, followed by nausea, vomiting, breast tenderness, and abdominal pain. During the six treatment cycles, dysmenorrhea was not reported. No change in body weight and blood pressure was observed during the study.¹⁹ In the study conducted by Barbosa *et al.* no alterations in body weight or laboratory evaluations were noted. Significant improvement in quality of life was observed, in terms of improvement in total Moos Menstrual Distress Questionnaire (MDQ) score. Further, the patients had a significant improvement in premenstrual complaints and symptoms.²⁰

A systematic review has suggested that headache that occurs with the use of oral contraceptives in the early cycles improves or disappears with continued use. There

was no evidence to support switching of one COC to another due to headache.²¹

Whether COCs exert a positive effect on bone mineral density (BMD) is debatable. A prospective, controlled, randomised study compared the effect of a low-dose 21/7 regimen gestodene/EE (75/20 µg) and an ultra-low-dose 24/4 regimen gestodene/EE (60/15µg) on bone turnover and BMD in young, fertile women. The study reported a positive impact of both regimens, compared with control group, on bone turnover. There was significant reduction in pyridinoline and deoxypyridinoline levels (markers of bone resorption) in both treatment groups from the third month of treatment.²²

Effect on haemostasis

Cardiovascular side effects are the most important potential adverse events associated with OC use. The incidence of thromboembolic events is directly related to the dose of estrogen. The important reason for reduction of the estrogen dose in COCs is based on the evidence that COCs are accountable for the development of a hyperclottable state.²³ A recent Cochrane review conducted that preparations containing lower doses of estrogen did not increase the arterial thrombotic risk, and the risk did not vary according to which progestogen type was used.²³

A 12-month study evaluated the effect of 24/4 regimen of gestodene 60 µg/EE 15µg on cycle control and haemostasis in 58 healthy women (age 19–47 years). Among the 20 women in whom haemostasis was evaluated, no changes in plasma fibrinogen concentrations or prothrombin fragment F112 were observed. There was a slight increase in thrombin-antithrombin III complexes after 6 and 12 months of COC use. After a year of COC use, antithrombin III activity significantly increased. However, there was no effect on concentrations of tissue plasminogen activator and plasminogen activator inhibitor. The study concluded that, COC containing low doses such as 15 µg EE do not affect haemostasis in healthy females.²⁴

Advantages of an ultra-low-dose COC

While choosing a COC regimen for a woman, it is recommended to select one with lowest dose of estrogen and progestogen to provide good cycle control and effective contraception. The selected regimen should be well-tolerated. Reducing the dose of estrogen has been suggested in many women as a strategy to manage the common side effects such as nausea, breast tenderness, bloating, fluid retention, and headache.²⁵ Considering the benefits of the ultra-low-dose COC, these may be suggested in women who experience side-effects associated with estrogen dose, such as nausea, breast tenderness, bloating and fluid retention, and headache. These may also be used in women for whom the lowest dose of estrogen is usually recommended, for instance in

women who have had history of nausea, edema or hypertension in pregnancy; those with uterine fibroids, fibrocystic breasts, heavy menses or migraines.²⁶

CONCLUSION

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