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Evaluation of extended and continuous use oral contraceptives

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Abstract: Oral contraceptives are classically given in a cyclic manner with 21 days of active pills followed by 7 days of placebo. In the past 4 years, new oral contraceptives have been introduced which either shorten the placebo time, lengthen the active pills (extended cycle), or provide active pills every day (continuous). These concepts are not new; extended and continuous pills were first studied in the 1960s and 1970s and have been provided in an off-label manner by gynecologists to treat menstrual disorders, such as menorrhagia and dysmenorrhea, and gynecologic disorders, such as endometriosis. Now that extended and continuous combined oral contraceptives are available for all patients, it is critical for providers to understand the physiology, dosing, side effects, and benefits of this form of oral contraceptive. This article reviews the history and the potential uses of the new continuous combined oral contraceptive.

Keywords: oral contraceptives, administration, dosage, adverse effects, menstrual disturbances

Introduction

Oral hormonal contraceptives (OCPs) were developed over 40 years ago as an effective, immediately reversible contraceptive. During this time, the doses of estrogen and progestin decreased, thus lessening the potential risk while maintaining efficacy. More recently the contraceptives have been altered to shorten or eliminate placebo pills to lessen menstrual symptoms. Combination hormonal contraceptives are typically taken orally, but transdermal and vaginal administration are also available.

The presence of cyclic bleeding is not essential for the contraceptive action of OCPs and studies indicate that many women are interested in reducing the frequency of their menstruation (den Tonkelaar and Oddens 1999; Edelman et al 2006; Trego 2007; Wiegratz et al 2004). Despite early research indicating that extended cycles were safe, until recently the pill was marketed exclusively in the 21 day active + 7 day placebo cycle format (Loudon et al 1977; Miller and Hughes 2003; Anderson and Hait 2003). Randomized trials have now proven the safety and efficacy of extended (24 active + 4 placebo, 84 active + 7 placebo) and continuous hormonal dosing (Coutinho et al 1995; Miller and Notter 2001; Archer et al 2006). This article will review the pharmacology of oral contraceptives and focus on studies evaluating the safety, efficacy, and patient satisfaction of continuous OCPs.

Pharmacology

Estradiol is the major estrogen produced by the ovary but its use is limited due to poor absorption when taken in a non-micronized form. The addition of an ethinyl group to the 17 position renders the species orally active and thus ethinyl estradiol is the most common estrogen available in modern OCPs. Mestranol, another orally active estrogen available in OCPs, is converted to ethinyl estradiol in the body. The original dose of ethinyl estradiol was higher than current medication; most modern OCPs

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contain 20–35 µg of ethinyl estradiol and offer comparable safety and efficacy and reduced incidence of adverse events (Speroff and DeCherney 1993).

Pharmacologic progestins were created by removing the 19 carbon from ethisterone, a derivative of testosterone. The 19-nortestosterone progestins used in OCPs are of two major types, called estranes and gonanes. Gonanes have greater progestational activity per unit weight than do estranes, requiring a lower dosing of gonanes for effectiveness in OCP formulations. Estranes correspond to first-generation progestins and include norethisterone, norethindrone, ethynodiol diacetate, lynestrenol, and norethynodrel. Gonane progestins are divided into two categories: the second-generation progestins levonorgestrel and norgestrel, and the third-generation progestins desogestrel, gestodene, and norgestimate. New progestins are being examined for contraceptive use including drospirenone, derived from spironolactone, an antimineralocorticoid medication; dienogest, a norethindrone-like structure that acts as an antiandrogen; and three 19-norprogesterone derivatives nesterone, nomegestrol acetate, and trimegestone (Sitruk-Ware 2006). The overall difference between progestin families in modern OCP formulations is minimal. OCPs are formulated to contain the lowest effective dose, and similar biologic effects are seen with various progestins; no studies have demonstrated that one progestin provides superior efficacy (Speroff and DeCherney 1993).

Side effect profiles related to OCPs vary somewhat based on type of the type of progestin. Less patient initiated discontinuation and improved cycle control with less intermenstrual bleeding has been reported with second- compared with first-generation progestins. Patient acceptability of third- and second-generation progestins is greater than that of first-generation preparations (Maitra et al 2008).

The primary contraceptive mechanism of the combination OCP is to prevent ovulation by inhibiting gonadotropin secretion at both the level of the pituitary gland and the hypothalamus. The estrogen component of OCPs directly inhibits follicle-stimulating hormone (FSH) secretion and thus limits the development of the dominant ovulatory follicle. The progestin component of the OCP profoundly suppresses luteinizing hormone (LH) secretion and thus reliably prevents the LH surge which triggers ovulation (Mishell et al 1977).

In a normally menstruating woman who is not taking contraceptive hormones, progesterone is only present in appreciable quantities during the luteal phase of the menstrual cycle, after the development of the endometrium. When combination OCPs are administered, the effect of

the progestational agent takes precedence over the estrogen component in the reproductive tract, and the endometrium demonstrates this progestin effect (Moyer and Felix 1998). The result is a thin, decidualized endometrium with atrophied glands that is not receptive to embryo implantation. Progestins also cause thick, impermeable cervical mucus, preventing sperm from reaching the uterine cavity, and decreases tubal mobility, altering the movement of sperm and oocytes through the fallopian tube (Johnson et al 2007; Rossmanith et al 1997).

Although progestin alone is an effective contraceptive, there are benefits when estrogen and progestin are combined in an OCP. By directly inhibiting FSH, estrogen contributes to the contraceptive efficacy of the OCP by limiting follicular development. In the endometrium, estrogen stimulation provides stability and may decrease irregular breakthrough bleeding seen with progestin only contraceptives (Mahmood et al 1998). Estrogen also potentiates the action of progestational agents, presumably by increasing the concentration of intracellular progestin receptors (Kastner et al 1990). This latter effect may decrease the progesterone dose required in the combination OCP.

OCP cycle formulations

The original OCP was designed to allow monthly bleeding. It was presumed that regular withdrawal bleeding was critical to increase acceptance of the OCPs. However, this bleeding is not a physiologic menstrual period. Physiologic menses occur due to estradiol-induced endometrial growth, followed by progesterone-induced decidualization of the endometrium, and bleeding with the withdrawal of progesterone and estradiol. With OCPs, the only portion of the cycle with unopposed estrogen occurs during the placebo week, when FSH is not suppressed and the ovary produces estradiol. The active pills provide a progestin and thus prevent future growth of the endometrium. By limiting or eliminating the placebo pills, the endometrium will not develop and withdrawal bleeding will not occur. With continuous hormonal contraceptives there is limited development of the endometrium. Although bleeding may occur with extended or continuous OCPs, due to atrophic changes in the endometrium, there is no typical endometrium to shed.

The concept of extended and continuous hormonal contraceptives is not new. The first investigation of an extended combination OCP regimen was performed in the 1970s (Loudon et al 1977). This non-randomized trial evaluated the effect of an extended cycle regimen of 84 days of a combination OCP containing lynoestrenol 2.5 mg

and ethinyl estradiol 50 µg on 196 women. No pregnancies occurred during the 1-year study period and 82% of women who completed the study reported that they welcomed the reduction in menstruation. Twenty-four percent of women reported breakthrough vaginal spotting during the first 3 months of the trial but this rate decreased to 4% during the last 3 months of use. The first randomized study evaluating an extended cycle regimen was conducted in 1993 (Cachri-manidou et al 1993). This multicenter study compared the acceptance of desogestrel 150 µg and ethinyl estradiol 30 µg dosed in a cyclic or extended regimen. There was significantly more breakthrough bleeding in the extended cycle group, but this decreased throughout the year and was significantly less in women who were using an OCP prior to enrolling in the trial. Significantly more women stopped the trial because of bleeding problems in the extended cycle group, while significantly more women stopped the trial because of headache in the standard cycle group. No significant differences were found in body weight changes, hemoglobin, or blood pressure between the two groups. After trials to confirm efficacy and safety, extended cycle oral contraceptives became available in 2003 (Miller and Hughes 2003; Anderson and Hait 2003).

The first randomized trial of combined continuous OCPs was published in 1995 (Coutinho et al 1995). This multicenter, international trial evaluated the acceptability, efficacy, and safety of levonorgestrel 250 µg and ethinyl estradiol 50 µg administered vaginally either cyclically or continuously. Nine hundred subjects were randomized to traditional cyclic administration or continuous administration for one year. Interestingly, four undesired pregnancies occurred in the cyclic administration group and none occurred in the continuous administration group; this difference was statistically significant ($p = 0.0486$).

Two continuous OCP trials were published in 2003 (Miller and Notter 2001; Kwiecien et al 2003). Miller et al evaluated 79 women randomized to receive cyclic or continuous oral levonorgestrel 100 µg and ethinyl estradiol 20 µg for 336 days (Miller and Notter 2001). No pregnancies were reported. Amenorrhea or infrequent bleeding was present in 68% of continuous users during the first three cycles and this increased to 88% during the last three cycles of the trial. There was no difference in adverse events, and blood pressure, weight and hemoglobin findings were not significantly different between groups. Kwiecien et al published a randomized trial assessing bleeding patterns and acceptability of cyclic versus continuous OCP dosing of oral levonorgestrel 100 µg and ethinyl estradiol 20 µg (Kwiecien et al 2003). Thirty-two women were randomized

and 28 participants (87%) completed the 168 day trial. No pregnancies occurred during the study period however one occurred in the continuous OCP group after completion of the study. The number of bleeding days based on menstrual diaries was less in the continuous group but did not reach statistical significance. The continuous group had significantly higher rates of amenorrhea and significantly decreased menstrual pain and bloating.

A single-treatment, multicenter, open-label Phase 3 trial evaluating the safety and efficacy of continuous dosing of levonorgestrel 90 µg and ethinyl estradiol 20 µg in 2134 women led to FDA approval of a continuous combined OCP in 2007 (Archer et al 2006). Fifteen pregnancies were attributed to method failure, giving a Pearl Index of 1.26. The most common side effect of amenorrhea was expected with continuous OCP; at pill pack 13 58.7% reported amenorrhea and 79.0% reported absence of bleeding. Subjects with bleeding decreased from 93.9% at pill pack 1 to 21.0% at pill pack 13; 860 subjects completed all 13 pill packs.

Efficacy

The most common question asked by patients is the effectiveness of the contraceptive in preventing pregnancy. With perfect use, cyclic oral contraceptives are highly effective; 0.3% of women have an unwanted pregnancy when taken perfectly for 1 year. Unfortunately, with typical use the rate rises to 8% of women in 1 year of OCP use (Trussell 2004). The most common risk with OCPs is imperfect use, typically due to “missed pills.” When pills are missed at start of the pack and the days without active pills are extended, the risk of ovulation may increase (Tayob et al 1990). Continuous OCPs would potentially lessen this risk by reducing the number of active pills missed when the start of the pill pack is delayed.

Efficacy studies of extended and continuous cycle OCPs demonstrate that these regimens are as effective as cyclic administration. The largest study to date evaluating an extended cycle regimen in 456 patients demonstrated a pregnancy rate of 0.9% compared with a 1.3% pregnancy rate in the standard cycle group over the course of 1 year (Anderson and Hait 2003). Two smaller randomized one year long studies of extended regimens reported no pregnancies in 99 and 198 patients (Coutinho et al 1995; Miller and Notter 2001). The largest study of continuous OCP users evaluated 2134 women, 19 of whom became pregnant during the 1-year study period. Fifteen of these pregnancies were attributed to method failure (Archer et al 2006). Another large study randomized 900 women to cyclic or continuous use for one year (Coutinho et al 1995). Four undesired pregnancies occurred

in the cyclic administration group and none occurred in the continuous administration group; this difference was statistically significant ($p = 0.05$). Two smaller studies randomizing cyclic and continuous use OCPs demonstrated no pregnancies in either group during the study period (Miller and Hughes 2003; Kwiecien et al 2003).

Limitations/side effects

The most commonly reported side effect with continuous or extended regimen OCP dosing is breakthrough vaginal bleeding. Studies evaluating this side effect have reported its presence to varying degrees. In a large trial of continuous oral contraceptives, 396 patients (18.5%) withdrew due to bothersome uterine bleeding, making this the most common reason to withdraw from the study (Archer et al 2006). A Cochrane review evaluated 6 randomized controlled trials with extended or continuous OCPs (Edelman et al 2005). Although the differences between the medications and duration of the studies limited comparison between trials, the authors concluded that bleeding patterns were either equivalent or improved with the extended or continuous dosing regimen. The extended or continuous cycle groups also fared better with respect to headaches, genital irritation, tiredness, bloating, and menstrual pain in the studies that evaluated these side effects. There were no overall differences observed in contraceptive efficacy, safety profiles, compliance, discontinuation rates or patient satisfaction between cyclic and continuous users.

Amenorrhea rates for the 3 largest studies are summarized in Table 1. Collectively these data indicate that most patients on continuous OCPs will obtain amenorrhea after 1 year of treatment but the exact incidence is difficult to quantify given the slightly different hormonal regimens used by each study. Additionally, the incidence of breakthrough bleeding and spotting is initially high with continuous dosing but appears to decrease consistently over time. Whether amenorrhea rates would continue to increase after one year of treatment is uncertain because no studies have evaluated treatment beyond one year. The total number of bleeding days is less with

continuous dosing than with traditional cyclic dosing although the timing of bleeding with continuous dosing will not typically occur at predictable intervals. Finally, the incidence of vaginal spotting was either increased or unchanged with continuous dosing in studies comparing continuous to traditional cyclic dosing (Miller and Notter 2001; Kwiecien et al 2003; Archer et al 2006).

Although breakthrough bleeding is a temporary problem for some women on continuous OCPs, providers can reassure women that this bleeding does not demonstrate an endometrial abnormality. Studies evaluating endometrial histology on continuously dosed OCPs have found reassuring results. A substudy of a large Phase 3 trial evaluated baseline and on therapy endometrial histology of 93 subjects taking continuous levonorgestrel 90 μg and ethinyl estradiol 20 μg (Johnson et al 2007). Endometrial biopsies were performed at baseline and after at least 6 months of treatment. Before treatment, 60% of subjects had a endometrial histology classified as proliferative; after 6 months of continuous OCP, most subjects (52%) had endometrial histology classified as other, indicating benign and inactive endometrium. Only 3 subjects had proliferative endometrium with continuous OCP use. No endometrial hyperplasia or malignancy was found in any biopsy specimen. Another substudy evaluated endometrial thickness on transvaginal ultrasound and endometrial biopsies of 11 women on continuous levonorgestrel 90 μg and ethinyl estradiol 20 μg and 7 women on a traditional 28 day cycle of the same hormonal combination (Miller and Notter 2001). All subjects had endometrial stripe measurements <5 mm and 88% of continuous use subjects had inactive or atrophic endometrial biopsies. In contrast, 60% of cyclic use subjects had proliferative endometrium on biopsy. No endometrial hyperplasia or malignancy was identified.

The resumption of menses after discontinuation of continuous OCPs has been shown to occur within 60 days for 94.7% of subjects; 75% had menses in 36 days or less (Davis et al 2008). In addition, in a small study, 81% of women achieved pregnancy within a year of discontinuation of the OCP (Barnhart et al 2006). This supports the theory that continuous OCPs, as with cyclic dosing, provides an effective and immediately-reversible contraceptive option for women.

Side effects with continuous combined OCPs were not increased when compared to cyclic OCPs (Coutinho et al 1995; Miller and Notter 2001; Kwiecien et al 2003). As expected with oral contraceptives, a modest number of subjects reported adverse effects with continuous OCPs in the Phase 3 trial such as abdominal pain (9.6%), back

Table 1 Amenorrhea rates in users of continuous oral contraceptives containing levonorgestrel in 3 large studies (each pill pack contained a 28-day supply)

	Pill packs 1–3	Pill pack 12–13
Coutinho (1995)	67.6%	87.5%
Miller (2003)	16%	72%
Archer (2006)	2.3%	58.7%

pain (10%), and headache (30%), although these effects were not compared to placebo or cyclic OCPs. Botherome uterine bleeding caused 18.5% of subjects to withdraw from the study. Rare serious adverse events included two subjects with cholecystitis, one thrombotic event, one ectopic pregnancy, one prolonged uterine bleeding, and one enlarged uterine fibroids (Archer et al 2006).

OCPs have several known metabolic effects including increased production of clotting factors resulting in increased risk of venous thromboembolism, increased gallstone formation during the first year of use, and increased risk of liver adenomas (Speroff and DeCherney 1993). Limited information is available on the metabolic effects of continuous or extended OCPs. One small study randomized 30 women to a cyclic versus extended regimen and found no differences in liver proteins, lipoproteins, and hemostatic variables at 0, 3, and 12 months (Cachrimanidou et al 1994). The small increased temporal exposure to synthetic hormones, associated with extended or continuous OCP use, is unlikely to result in significant metabolic differences compared with traditional cyclic administration.

Noncontraceptive benefits

Clearly, extended and continuous oral contraceptives are effective in lessening menstrual bleeding, but these medications may also lessen other menstrual symptoms. It is reported that 20%–40% of women have significant menstrual-related symptoms, adversely affecting over 2.5 million women in the US (Kjerulff et al 1996). Table 2 summarizes menstrual conditions that may be improved with extended or continuous cycle OCPs. Several studies have evaluated the utility of extended and continuously dosed OCPs for reducing menstrual symptoms including dysmenorrhea and premenstrual symptoms. One study demonstrated that of 267 patients who initiated an extended regimen for menstrual symptoms, 64% preferred the extended regimen while 21% discontinued OCPs and 14% returned to a standard OCP regimen (Sulak et al 2002). Another study of 50 patients

Table 2 Conditions that may be improved with continuous and extended cycle oral contraceptives

Dysmenorrhea (Archer 2005; Vercellini 2003)
Menstrual migraine (Archer 2005; Vercellini 2003)
Premenstrual syndrome (Archer 2005; Vercellini 2003)
Menorrhagia (Archer 2005; Vercellini 2003)
Ovarian cysts (Edelman 2007)
Endometriosis (Schneider 1999)
Pelvic pain (Schneider 1999)

with menstrual-related problems including dysmenorrhea, menorrhagia, premenstrual-type symptoms, and menstrual migraines found that 74% stabilized on an extended regimen cycle OCP regimen while 26% either discontinued OCPs or returned to the standard regimen (Sulak et al 1997).

In addition to lessening menstrual symptoms, continuous oral contraceptives may be effective at reducing symptoms related to other gynecologic conditions such as ovarian cysts, pelvic pain, and endometriosis. Continuous OCPs effectively suppress ovarian activity and ovulation as evidenced by one study in which 91.7% of women on continuous OCPs had no active follicles seen on transvaginal ultrasound (Archer et al 2005). An Italian study evaluated continuously dosed OCPs as a treatment for dysmenorrhea associated with endometriosis (Vercellini et al 2003). This study evaluated women with surgically treated endometriosis who had persistent dysmenorrhea on cyclic OCPs. A significant reduction in the mean dysmenorrhea visual analog scale was noted with continuous OCP therapy and of the 50 women who completed the trial, 26% reported being very satisfied and 54% reported being satisfied with this treatment.

Patient perspectives

Studies indicate that regularly cycling women are interested in reducing the frequency of menstruation. A Dutch telephone survey evaluating attitudes towards menstruation in reproductive aged women demonstrated that 80.5% preferred less painful menses, shorter menses, less heavy menses and/or amenorrhea to their current cycle. Most of the menstruating women in all age groups preferred to have a bleeding frequency of less than once a month or never, and this result was more significant in older women and in women using OCPs (den Tonkelaar and Oddens 1999). A similar German survey of 1195 women aged 18–49 found that 26%–35% of the women preferred monthly bleeding, while 37%–46% wished never to bleed. Women who preferred fewer menses reported a desire for fewer severe menstrual complaints, better hygiene, higher quality of life, and less blood loss. Women who preferred monthly bleeding cited concerns such as fear of pregnancy, infertility and adverse events and a belief that menstruation is natural (Wiegatz et al 2004). Finally, a survey conducted in the US indicated that 69% of women did not like their menstrual period and 58% preferred a menstrual frequency of every 3 months or never. However, only 29% of black women would consider a birth control method to stop their menstrual periods compared with 49% of white women (Edelman et al 2007).

For some careers, the cessation of menses is advantageous for women. Any job which limits hygiene, such as active-duty military, may be simplified by reducing menses. More than 60% of active-duty military women state that menstrual symptoms adversely affect their work (Schneider et al 1999).

Despite relatively high patient drop-out rates in some studies evaluating extended regimen and continuous OCPs, high patient satisfaction has been consistently reported. In one of the original studies evaluating extended regimen OCPs, 91% of women who completed the trial refused to revert back to a standard monthly dosing regimen due to their satisfaction with the extended cycle regimen (Loudon et al 1977). Another study evaluating an extended regimen showed that most patients rated their overall satisfaction with the extended cycle OCP regimen as good to excellent and stated they would choose to have fewer menstrual periods after the completion of the study (Anderson and Hait 2003). For continuous use OCPs, patient satisfaction is as high as with cyclic users; 78.1% of women planned to continue using continuous OCP dosing at completion of the study and 18.8% planning to switch to cyclic use (Kwiecien et al 2003). Similarly, 67.9% of cyclic users planned to continue cyclic use and 21.4% planned to try continuous use.

Concern about possible pregnancy appears to be low in patients taking continuous OCPs, with 4 out of 79 patients citing "a little" concern in one study (Kwiecien et al 2003). Clinical experience and study surveys indicate that some women prefer to have monthly withdrawal bleeding to provide reassurance that they are not pregnant. Appropriate counseling on the contraceptive efficacy of continuously dosed OCPs would likely reassure many of these patients. Pregnancy tests can certainly be offered to patients on continuous OCPs; however, many other contraceptive methods cause menstrual irregularity or suppression and routine pregnancy tests are not medically indicated for these patients. Importantly, OCPs are not teratogenic and do not increase the risk of fetal malformations.

Finally, a survey evaluating physician attitudes towards extended or continuous OCP dosing in adolescents reveals that 90% of surveyed physicians reported ever prescribing extended or continuous dosing regimens (Gerschultz et al 2007). Gynecologists were more likely than other specialties to prescribe frequent extended cycles or continuous regimens and 33% reported that extended cycles make up greater than 10% of their total OCP prescriptions. The most common reasons for prescribing extended or continuous regimens were to accommodate patients' requests to induce amenorrhea for specific events (82%), to obtain fewer menses per year (72%), and to treat menorrhagia (68%), dysmenorrhea (65%), or endometriosis (62%).

Conclusions

Continuous OCPs are a safe and reliable form of birth control. The metabolic, hormonal, and endometrial effects are similar in cyclic and continuous OCP users. The most commonly reported side effect of continuous OCP dosing is irregular vaginal bleeding, but the incidence of this decreases over time and most patients will obtain amenorrhea after 1 year of treatment. Continuous OCP dosing has proven efficacious in women with menstrual symptoms and dysmenorrhea, although larger randomized studies are indicated. Patient satisfaction with both cyclic and continuous OCP use is high. Candidates for continuous OCP dosing include anyone who is a candidate for traditional cyclic OCPs dosing; no additional contraindications exist. Additionally, there is no temporal limitation to the use of continuous OCPs as excellent safety data exist for endometrial histology. Women who wish to limit cyclic bleeding, for personal or medical reasons, are excellent candidates for continuous OCPs. It is appropriate for practitioners to offer both dosing regimens for any patient interested in starting an OCP and continuous dosing may be preferable for patients with dysmenorrhea or other menstrual symptoms.

Guidelines

- Extended and continuous cycle OCPs have equal efficacy to classic 21 + 7 cyclic OCPs.
- Although bleeding patterns, compared with classic cyclic OCPs, have been shown to be equivalent or improved with extended or continuous cycle OCPs, bothersome uterine bleeding is the most common reason for withdrawal from studies. Patients can be advised of this potential side effect.
- There is no increased concern of endometrial abnormalities with extended or continuous OCPs.
- Extended or continuous OCPs decrease menstrual symptoms, including dysmenorrhea and premenstrual symptoms.
- Women who desire fewer menses, for occupational or personal reasons, may be considered for extended or continuous OCPs.

Disclosures

Neither author has any conflicts of interest to disclose.

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