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Bleeding patterns and menstrual-related symptoms with the continuous use of a contraceptive combination of ethinylestradiol and drospirenone: a randomized study

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Abstract

Background: The objective of this study was to compare bleeding patterns of women using a contraceptive combination of 30 mcg ethinylestradiol (EE) and 3 mg drospirenone (DRSP) continuously or cyclically. Menstrual-related symptoms were also evaluated.
Study Design: This open, prospective, randomized study evaluated 78 women using the EE/DRSP combination continuously for 168 days or for six 28-day cycles, each followed by a 7-day hormone-free interval. A diary with pre-established scales was used to assess the frequency and intensity of bleeding and menstrual-related symptoms.
Results: Amenorrhea increased with continuous use; 62.2% of women with continuous use were amenorrheic at the end of treatment (95% CI: 46.6–77.8%). Dysmenorrhea, headache, acne, nausea, edema and increased appetite improved significantly in the continuous-use group, and mastalgia and edema in the cyclic-use group ($p<.05$). Six subjects in the continuous-use group (15.4%) and three in the cyclic-use group (7.7%) discontinued due to adverse events.
Conclusions: Continuous use was associated with amenorrhea and fewer menstrual-related symptoms compared to cyclic use.

Keywords: Oral contraceptive; Ethinylestradiol; Drospirenone; Continuous use; Bleeding patterns

1. Introduction

The conventional use of combined oral contraceptives (COCs) generally consists of cyclic administration for 21 days followed by a 7-day hormone-free interval during which bleeding occurs as a result of hormone deprivation. Currently, the benefits of this monthly pause in the use of OCs have been questioned, since, from a biological point of view, the artificial bleeding resulting from hormone deprivation does not appear necessary and may be associated with menstrual-related syndromes [1–3]. For some women, monthly bleeding is undesirable, not only because of the symptoms that appear around this time but also for personal reasons such as convenience and practicality [4]. Consequently, alternative regimens have been introduced, including continuous contraception or regimens in which the number of active pill days is extended. In both regimens, the objective is to avoid problems related to the monthly pause in contraceptive use and to improve compliance with the method, thereby increasing satisfaction and enhancing the quality of life of women who choose to use COC [5–8].

The majority of studies evaluating the continuous use of COCs have focused on bleeding patterns [9,10], since most women opting for this contraceptive regimen do so because they wish to eliminate their bleeding episodes. Others, however, extend COC use in an attempt to improve symptomatology experienced during the pause in OC use [5].

The effects of modern contraceptives in which low doses of estrogen are combined with selective progestogens have

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also been studied in extended regimens. Similarly, the antiandrogenic and antimineralocorticoid properties of drospirenone have been evaluated, with results showing that amenorrhea rates of over 80% in continuous-use regimens are associated with a reduction in symptoms such as mastalgia, edema, swelling, seborrhea and dysmenorrhea [11,12]. Other studies carried out recently with the contraceptive combination of 3 mg of drospirenone (DRSP) and 30 mcg of ethinylestradiol (EE) also showed that the extended use of this COC for up to 1 year effectively controlled menstrual-related symptoms [13,14]. It should be emphasized that the abovementioned studies evaluated women using the EE/DRSP combination continuously in nonrandomized studies [12–14]. Due to the lack of comparative, randomized studies involving the EE/DRSP combination in a continuous regimen, the proposal of the present study was to compare bleeding patterns in users of a COC containing EE and DRSP either in a continuous regimen or during cyclic use with a 7-day pause after 28 days of use and to assess the effects of these two regimens on menstrual-related symptoms.

2. Materials and methods

2.1. Study design

An open-label, prospective, randomized clinical trial was carried out in 78 women randomly allocated to use a COC containing EE (30 mcg) and DRSP (3 mg) either continuously (continuous-use group) or with a 7-day pause (cyclic-use group).

Continuous use consisted in the daily administration of the contraceptive pill uninterruptedly for 168 days. Cyclic use consisted in the daily administration of the same contraceptive pill for six 28-day cycles with a 7-day hormone-free interval at the end of each cycle. The subjects were randomized into two groups of equal size (39 subjects in each group) to receive the combination of 30 mcg EE and 3 mg DRSP either continuously (continuous-use group) or cyclically (cyclic-use group). For the randomization process, a computer-generated list was created using the Random Allocation software program, version 1.0, May 2004, originally designed by Dr. M. Saghali, University of Medical Sciences, and freely available to the public. The subjects were allocated sequentially according to the pre-established randomization number, using sequentially numbered opaque envelopes which contained the randomization number. The randomization process and the statistic analysis were done by an independent specialist unrelated to the study.

The protocol was approved prior to study initiation by the internal review boards of each participating center, and the study was conducted in accordance with the directives of the Brazilian regulatory authorities (ANVISA), with the guidelines of Good Clinical Practice established by the International Conference on Harmonization (ICH) and with the principles defined in the Declaration of Helsinki. All women were informed with respect to the nature of the study and voluntarily agreed to participate by signing an informed consent form.

2.2. Participants

Women at three Brazilian health care centers, who were sexually active, requesting a contraceptive method and not currently using any form of hormonal contraception or an IUD, were eligible to participate in the study. The inclusion criteria consisted of age 18–35 years, body mass index (BMI) of 19–30 kg/m^2, a minimum of 8 years of schooling, ability to understand oral and written instructions, and willingness to comply with the study requirements and to sign the informed consent form. Women were not admitted to the study if they were pregnant (either suspected or confirmed pregnancy), if they had an abnormal Pap smear, a personal history of genital or breast neoplasia, cardiovascular disease, arterial hypertension, venous or arterial thromboembolism, diabetes mellitus, acute or chronic hepatopathies, or alcoholism. In addition, women who had been using hormonal contraceptives in oral, injectable or implant form in the 2 months preceding the study and those in concomitant use of barbiturates, hydantoins, carbamazepine, phenylbutazone, meprobamate, rifampicin or any other drugs capable of interacting with OCs were excluded from the trial.

The woman's medical history was recorded and a complete physical and gynecological exam was carried out, including sampling for cervicovaginal cytology. The following laboratory tests were requested as safety parameters: complete blood count, fasting glucose, AST, ALT, total and fractionated bilirubin, gamma-glutamyl transferase, urea, creatinine, alkaline phosphatase, TSH and free T4 and a beta-hCG pregnancy test.

Two weeks later, if the test results were satisfactory and the inclusion and exclusion criteria were met, the women were randomized and instructed to initiate use of the COC containing EE (30 mcg) and DRSP (3 mg) on the first day of their next menstrual period and to use it either continuously or with a 7-day interval without hormone use at the end of each 28-day period. The study drug was supplied in packs of 28 pills and each patient received a total of six pill packs.

Each woman was requested to complete an individual diary specifically designed to record information on the date of initiation of pill use, the number of forgotten pills, the occurrence of bleeding and its intensity, and any symptoms experienced during the evaluation period.

The women who were randomized to continuous treatment used the contraceptive pill for 24 consecutive weeks, returning to the clinic every 4 weeks for a follow-up visit. In the group of women using the pill cyclically, the pills were taken in six consecutive 28-day cycles with a 7-day hormone-free interval between each cycle. These women returned for follow-up visits every 5 weeks. At all visits, information on bleeding and symptoms recorded in the woman's diary was evaluated, any questions were answered and any complaints or adverse events were recorded.