ELSEVIER

Contraception 73 (2006) 30–33

Contraception

Original research article

Prospective, open-label, noncomparative study to assess cycle control, safety and acceptability of a new oral contraceptive containing gestodene 60 μg and ethinylestradiol 15 μg (Minesse®)

Ione C. Barbosa[a,*], Carlos Isaia Filho[b], Dirceu Faggion Jr.[c], Edmund Chada Baracat[d]

[a]*Maternidade Climério de Oliveira, Universidade Federal da Bahia, 40055-150 Salvador, Bahia, Brazil*
[b]*Centro de Medicina Reprodutiva Dr. Carlos Isaia Filho, 90510-040 Porto Alegre, RS, Brazil*
[c]*DFJ Clínica Médica, 03062-000 São Paulo, Brazil*
[d]*Department of Obstetrics and Gynecology, Hospital São Paulo, Federal University of São Paulo, 04037-003 São Paulo, Brazil*

Received 27 April 2005; accepted 4 June 2005

Abstract

Objective: A prospective, open-label, noncomparative, multicenter study was carried out in 163 women aged 18–39 (mean 25±5 years), who used an ultra-low-dose oral contraceptive pill (OCP) containing gestodene (GTD) 60 μg/ethinylestradiol (EE) 15 μg for 6 months. The objective of the study was to evaluate the acceptability, safety, bleeding patterns and premenstrual symptomatology in these women.

Methods: Patients used the OCP from Days 1–24, followed by a 4-day pill-free interval from Days 25–28 of the menstrual cycle. Physical and gynecological examinations were carried out at baseline and after 3 and 6 months, at which time blood pressure, weight, hemoglobin, hematocrit, SGOT, SGPT and urinalysis were also assessed. The Moos Menstrual Distress Questionnaire (MDQ) was completed on three consecutive days (Days 25–27 of the cycle) at baseline and at the end of the third and sixth cycles. Patients kept a menstrual diary throughout the study.

Results: A total of 146 women completed the study. Ten women discontinued because of adverse events and one undesired pregnancy occurred during treatment. No adverse metabolic effects were observed. The adverse event most frequently reported was breakthrough bleeding, which diminished, however, as the time of OC use increased. Cycle length and duration of bleeding decreased significantly with OC use ($p<.01$ and $p<.05$, respectively, after 6 months). Intensity of menstrual bleeding tended to decrease with OC use, but this difference was not statistically significant. Systolic and diastolic blood pressure were significantly lower after 6 months of OC use compared to baseline ($p<.02$). No alterations were recorded in body weight or laboratory evaluations. Statistically significant changes were found both in the total MDQ score and in several of the factors evaluated, and patients showed a statistically significant improvement in well-being with respect to premenstrual complaints and symptoms.

Conclusion: This OC regimen is safe, well-accepted and well-tolerated, affects menstrual patterns beneficially by reducing both the intensity and duration of bleeding, provides good cycle control and improves premenstrual symptomatology.

Keywords: Contraceptives; Moos Menstrual Distress Questionnaire; Ethinylestradiol; Gestodene; Bleeding patterns

1. Introduction

Over the last 30 years, the development of oral contraceptives (OCs) has concentrated on reducing the dose of estrogen and progestogen with the objective of maintaining contraceptive efficacy while improving the drug safety and tolerability profile [1,2]. Among the newly developed progestogens, gestodene (GTD), a levonorgestrel derivative, exerts a more selective progestational action that improves cycle control, reducing metabolic changes and adverse effects while efficiently preventing pregnancy [3].

More recently, an ultra-low-dose contraceptive formulation containing 60 μg GTD and 15 μg ethinylestradiol (EE) was introduced with a view to offering the lowest available daily dose regimen in an oral combined monophasic contraceptive while maintaining contraceptive efficacy and cycle control [4,5]. The combination of 60 μg GTD and 15 μg EE results in a 25% reduction in the daily dose of the EE component and a 20% reduction in the GTD component

* Corresponding author. Tel.: +55 71 3242 4014.
E-mail address: barbosaic@terra.com.br (I.C. Barbosa).

0010-7824/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2005.06.057

compared to the newest combined monophasic contraceptives that contain 20 μg EE.

Epidemiological studies estimate that approximately 75% of women with regular menstrual cycles experience some premenstrual symptoms [6,7], and the great majority of these women do not require psychiatric treatment [7].

It is well known that poor cycle control and tolerability are the main reasons for the irregular use of contraceptives [8] which may lead to a reduction in contraceptive efficacy [9].

This prospective, open-label, noncomparative study was therefore conducted to assess acceptability, safety, bleeding patterns and premenstrual symptomatology in women using an oral contraceptive pill (OCP) containing GTD 60 μg/EE 15 μg.

2. Materials and methods

The study was carried out in four Brazilian centers following approval by the institutional review boards of the centers involved and was performed in compliance with the Helsinki Declaration. All volunteers gave their signed consent prior to enrollment in the study.

One hundred and sixty-three healthy outpatients of 18 to 39 years of age, who had had regular menstrual cycles (21–35 days) in the 3 months preceding enrollment, were included in the study. Patients used the OCP from Days 1 to 24 of the cycle, followed by a 4-day pill-free interval from Days 25 to 28 of the menstrual cycle, during six consecutive cycles. During the study, the use of other sex hormones or any drug such as isotretinoin that could alter the EE concentration was prohibited.

Patients were assessed during one control cycle and followed up during six treatment cycles (28 days/cycle). Complete clinical and gynecological evaluations, including breast examination, laboratory evaluations (hemoglobin, hematocrit, SGOT, SGPT and urinalysis) and Papanicolaou smears were carried out prior to the initiation of treatment and after the sixth cycle of OCP use. During the study period, the patients filled out self-assessment cards daily in which they reported pill intake, dates of any missed pills, menstruation, intermenstrual bleeding or spotting, any other signs or symptoms and any concomitant medication. During Cycle 3, patients underwent a physical examination at which blood pressure was monitored, and weight was registered. Data that had been recorded on the self-assessment card during the period since the previous visit were collected, and the occurrence of any adverse event was verified.

Quality of life was assessed using the self-administered Moos Menstrual Distress Questionnaire (MDQ), models C and T. Information at baseline was provided by patients who responded to the MDQ, model C, with retrospective information on the symptoms experienced during their previous cycle. During treatment, patients filled out the T model of the questionnaire during three consecutive days following completion of Blister 3 of the oral monophasic combination of EE 15 μg/GTD 60 μg (Days 25, 26 and 27) and after Blister 6 (Days 25, 26 and 27).

Statistical analysis was carried out on the combined data obtained from all patients at all the research centers. A descriptive analysis of age, weight, systolic and diastolic blood pressure, presence or absence of premenstrual syndrome, duration of the menstrual cycle, duration and intensity of withdrawal bleeding and intermenstrual bleeding was performed.

Student's *t* test for paired variables was used to analyze the duration of the menstrual cycle and the occurrence of withdrawal bleeding between the basal period and the end of the third and sixth cycles of treatment. The chi-square test was used to analyze the intensity of menstrual bleeding at baseline and at the end of the third and sixth treatment cycles. Quality of life was assessed by applying the Wilcoxon test for comparison of premenstrual symptoms reported in the MDQ at baseline and at the end of the third and sixth treatment cycles.

3. Results

Between September 2001 and August 2003, 163 women aged between 18 and 35 years (mean 25 years old) were enrolled in the study and considered for inclusion in the efficacy and safety assessment. Of the 163 women initially assessed, 17 (10%) withdrew prematurely from the study. Reasons for discontinuation were adverse effects (10 patients), loss to follow-up (4 patients), protocol violations (2 patients) and late enrollment in the study (1 patient). Table 1 lists the adverse effects that led to discontinuation of treatment.

With respect to the two patients who became pregnant during the study, one did not initiate pill use since pregnancy was detected by transvaginal sonography during the screening phase. The second patient had a positive β-hCG test during the fifth cycle of use, although she reported not having missed any pills since enrollment in the study.

3.1. Cycle control

A statistically significant reduction in the duration of the menstrual cycle was observed after three and six treatment cycles as compared to basal values ($p<.01$). However, no

Table 1
Adverse effects that led to discontinuation of treatment

Adverse effect	Number of cases
Amenorrhea*	3
Pregnancy**	2
Nausea and vomiting	2
Nausea, vomiting, migraine and dizziness	1
Nausea and dizziness	1
Mild hypertension	1

* The possibility of pregnancy was investigated and discarded in all cases.

** One pregnancy was detected during screening, and pill use was not initiated.

Table 2
Reduction in mean cycle length — comparison between periods

	N	Mean cycle length (days)	p*
Baseline	133	29.4	.001
Cycle 3	133	27.9	
Baseline	132	29.4	.001
Cycle 6	132	27.9	
Cycle 3	126	27.8	NS
Cycle 6	126	27.8	

* Student's *t* test for paired group was used.

statistically significant difference was observed between the third and the sixth treatment cycles (p=1.0) (Table 2).

A reduction in the duration of bleeding was observed in the comparisons between baseline (n=133, mean 4.4), Cycle 3 (n=133, mean 3.8) and Cycle 6 (n=132, mean 3.8) (p<.05).

A reduction in bleeding intensity was seen in 43% of the 132 patients who were assessed at baseline and at Cycle 3, whereas 53% of patients experienced no change in bleeding intensity and only 3.8% of the patients reported an increase in menstrual flow. In comparison, at the end of the sixth cycle, 49% of the patients presented a reduction in bleeding intensity, while bleeding remained unchanged in 48% and only 3% of patients reported an increase in bleeding intensity. Due to the methodology used, it was not possible to conclude whether these findings were statistically significant.

Fifty-three patients experienced a total of 150 episodes of breakthrough bleeding throughout the study period (an average of 2.8 episodes per patient). It should be pointed out that 40% of these episodes were concentrated in the first treatment cycle, and breakthrough bleeding progressively diminished throughout the six cycles of OCP use (Fig. 1).

Twelve patients experienced colpitis, eight of whom already had the condition before entering the study. The condition did not worsen in any of these women during the study and in all cases colpitis responded to specific pharmacological treatment.

3.2. Quality of life

Of the 163 patients assessed in this study, a subgroup of 144 patients answered the MDQ prior to the initiation of treatment and at the end of the third and sixth cycles of OCP use.

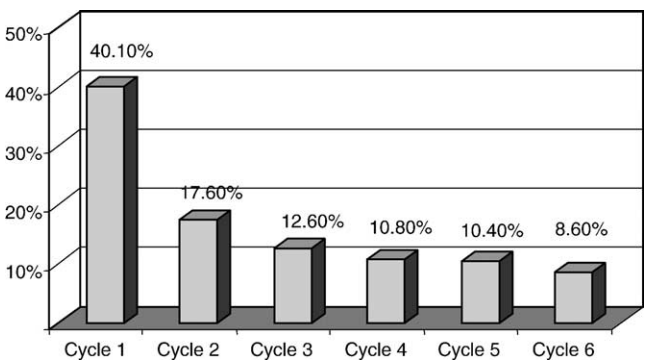

Fig. 1. Breakthrough bleeding throughout the six treatment cycles.

Table 3
Evolution of the MDQ scores during the premenstrual phase vasal vs. Cycle 6

Domain	Evolution	p*
Pain	Improvement	<.001
Concentration	Improvement	.01
Behavior changes	No change	.05
Autonomic reactions	No change	.36
Fluid retention	Improvement	<.001
Negative affect	Improvement	<.001
Vigilance	Improvement	<.001
Control	Improvement	.04
Total score	Improvement	<.001

* Wilcoxon test for each corresponding pair.

Following three treatment cycles, patients' premenstrual signs and symptoms were analyzed in relation to the eight domains covered by the MDQ, and significant changes were noticed in the sum of the scores for the domains *fluid retention* (p<.0001), *negative affect* (p<.0001), *vigilance* (p=.02), *control* (p<.04) and *total score* (p<.001) in relation to baseline assessment. After six cycles, a significant improvement was observed in the total score (p<.001) and in the sum of the scores for the majority of the domains, except *behavior change* and *autonomic reactions* (Table 3).

With respect to appetite change, which was also assessed in the patients by means of a specific item in the MDQ, scores after the third treatment cycle demonstrated a statistically significant difference when compared to the baseline assessment (p<.001) and when compared to data collected at the end of the sixth treatment cycle (p<.04).

3.3. Safety

Of the 163 patients assessed, 162 took at least one dose of the study medication. Of these, 95 reported more than one adverse event, totaling 254 events. Considering the occurrence of each event in a patient in a noncumulative way, the most frequent adverse events in relation to the study population were breakthrough bleeding (53 patients — 33%), amenorrhea (12 patients — 7.4%); colpitis (12 patients — 7.4%); headache (11 patients — 6.8%); delayed menstruation (7 patients — 4.3%); nausea (7 patients — 4.3%) and anemia (7 patients — 4.3%). No other clinically relevant occurrence was observed in the pretreatment period or during the six treatment cycles. No change in weight was observed during the study period.

4. Discussion

In this study, the ultra-low-dose combination of GTD 60 μg/EE 15 μg proved to be both safe and efficacious in maintaining cycle control. Patients had already experienced a reduction both in cycle length and in the duration of withdrawal bleeding by the third treatment cycle. A significant reduction in bleeding intensity was also ob-

served. These results are in agreement with reports in the literature on the use of GTD/EE combinations [4,5] and are predictable since the use of the GTD/EE combination for 24 days is known to lead to substantial endometrial suppression [10] and to confer a beneficial effect in terms of reducing the intensity and the duration of menstrual bleeding, while offering good cycle control.

The number of patients presenting breakthrough bleeding was greater in the first treatment cycle and decreased consistently throughout the treatment period. This positive development was expected with the use of low-dose contraceptives containing GTD [1,3,11–13].

The GTD 60 μg/EE 15 μg combination proved to have a good safety profile with a low rate of estrogen-related adverse effects such as headache, mastalgia and nausea, and these results are in agreement with reports from other studies on low-dose contraceptives [5,12,14]. There was only one case of mild arterial hypertension that reverted following the discontinuation of treatment and did not require specific medication. The reduction in the estrogen and progestogen content of OCs has lowered the risk of cardiovascular, cerebrovascular and thromboembolic disease [15–17].

One pregnancy occurred during the use of this contraceptive combination, and it was not possible to establish a direct relationship between the pregnancy and drug failure. According to the literature, in 16954 cycles assessed using specific methodology, the cumulative accidental pregnancy rate with the use of the GTD 60 μg/EE 15 μg combination was 0.0019 in 12 cycles and 0.033 in 19 cycles [5].

The results from the group of patients who answered the MDQ on the day preceding withdrawal bleeding already showed a positive variation in the domains of *fluid retention*, *negative affection*, *vigilance*, *control* and *total score* at the end of three cycles of pill use. This positive evolution continued until Cycle 6 when the majority of the domains and menstrual symptoms measured, including appetite change, which was assessed using a specific item in the MDQ, showed a positive evolution.These data were evaluated using the MDQ, which is a validated analysis tool [18,19], and results suggest that the use of this oral monophasic combination led to an improvement in quality of life.

In conclusion, the findings of this prospective study show that this ultra-low-dose combination of GTD 60 μg/EE 15 μg is safe, well tolerated, and exerts efficient cycle control, leading to a reduction in the number of bleeding days and in the intensity of withdrawal bleeding.

In addition, the use of this oral monophasic combination led to a statistically significant improvement in quality of life, as shown by the positive changes in the majority of premenstrual complaints and symptoms measured using the modified MDQ.

Acknowledgment

The financial support of Laboratórios Wyeth-Whitehall Ltda is gratefully acknowledged.

References

[1] Speroff L, De Cherney A. Evaluation of a new generation of oral contraceptives. The Advisory Board for the New Progestins. Obstet Gynecol 1993;81:1034–47.
[2] Fotherby K, Caldwell AD. New progestogens in oral contraception. Contraception 1994;49:1–32.
[3] Wilde MI, Balfour JA. Gestodene. A review of its pharmacology, efficacy and tolerability in combined contraceptive preparations. Drugs 1995;50:364–95.
[4] Cycle control, safety and efficacy of a 24-day regimen of gestodene 60 microg/ethinylestradiol 15 microg and a 21-day regimen of desogestrel 150 microg/ethinylestradiol 20 microg. Eur J Contracept Reprod Health Care 1999;4(Suppl 2):17–25.
[5] The safety and contraceptive efficacy of a 24-day low-dose oral contraceptive regimen containing gestodene 60 microg and ethinylestradiol 15 microg. Eur J Contracep Reprod Health Care 1999; 4(Suppl 2):9–15.
[6] Johnson SR. The epidemiology and social impact of premenstrual symptoms. Clin Obstet Gynecol 1987;30(2):367–76.
[7] Steiner M. Premenstrual syndromes. Annu Rev Med 1997;48: 447–55.
[8] Winkler UH, Ferguson H, Mulders JA. Cycle control, quality of life and acne with two low-dose oral contraceptives containing 20 microg ethinylestradiol. Contraception 2004;69:469–76.
[9] Korver T, Goorissen E, Guillebaud J. The combined oral contraceptive pill: what advice should we give when tablets are missed? Br Obstet Gynaecol 1995;102:601–7.
[10] Oosterbaan HP. An open-label study of the effects of a 24-day regimen of gestodene 60 microg/ ethinylestradiol 15 microg on endometrial histological findings in healthy women. Eur J Contracept Reprod Health Care 1999;4(Suppl 2):3–8.
[11] Lammers P, Berg M. Phase III clinical trial with a new oral contraceptive containing 150 micrograms desogestrel and 20 micrograms ethinylestradiol. Acta Obstet Gynecol Scand 1991;70: 497–500.
[12] Sullivan H, Fumiss H, Spona J, Elstein M. Effect of a 21-day and 24-day oral contraceptive regimens containing gestodene (60 microg) and ethinyl estradiol (15 microg) on ovarian activity. Fertil Steril 1999;72:115–20.
[13] Dursterberg B, Ellman H, Muller U, Rower E, Muhe B. A three-year clinical investigation into efficacy, cycle control and tolerability of a new low-dose monophasic oral contraceptive containing gestodene. Gynecol Endocrinol 1996;10:33–9.
[14] Fruzzetti F, Genazzani AR, Ricci C, De Negri F, Bersi C, Carmass F. A 12-month clinical investigation with a 24-day regimen containing 15 microg ethinylestradiol plus 60 microg gestodene with respect to hemostasis and cycle control. Contraception 2001;63:303–7.
[15] Lewis MA, Spitzer WO, Heinemann LA, MacRae KD, Bruppacher R, Throrogood M. Third generation oral contraceptives and risk of myocardial infarction: an international case-control study. Transnational Research Group on Oral Contraceptives and the Health of Young Women. BMJ 1996;312:68–90.
[16] Lewis MA, Spitzer WO, Heinemann LA, MacRae KD, Bruppacher R. Lowered risk of dying of heart attack with third generation pill may offset risk of dying of thromboembolism. BMJ 1997;315: 679–80.
[17] Rowlands S. Newer progestogens. J Fam Plann Reprod Health Care 2003;29:13–6.
[18] Ross C, Coleman G, Stojanovska C. Factor structure of the modified Moos Menstrual Distress Questionnaire: assessment of prospectively reported follicular, menstrual and premenstrual symptomatology. J Psychosom Obstet Gynaecol 2003;24:163–74.
[19] Borenstein J, Yu HT, Wade S, Chiou CF, Rapkin A. Effect of an oral contraceptive containing ethinyl estradiol and drospirenone on premenstrual symptomatology and health-related quality of life. J Reprod Med 2003;48:79–85.