ORIGINAL RESEARCH—WOMEN'S SEXUAL HEALTH

Preliminary Study on the Effect of Four-phasic Estradiol Valerate and Dienogest (E2V/DNG) Oral Contraceptive on the Quality of Sexual Life

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ABSTRACT

Introduction. A new oral contraceptive containing the natural estrogen estradiol and a 19-nortestosterone derivate dienogest (DNG) in a four-phasic 28-day regimen may be used by women.

Aim. To investigate the quality of sexual life of healthy women on estradiol valerate and DNG (E2V/DNG) oral contraceptive.

Methods. Fifty-seven women (age range 18–48 years) were enrolled. The Short Form-36 (SF-36) questionnaire to assess quality of life (QoL) was administered at baseline and at the 26th day of both the 3rd and 6th cycles of oral contraceptive (OC) intake. The Short Personal Experience Questionnaire (SPEQ) to measure the change of sexual behavior was used at the 2nd, 7th, 14th, 21st, 26th, and 28th days of the baseline cycle, as well as at the same days of both the 3rd and 6th cycle of contraceptive intake.

Main Outcome Measure. The SF-36 and the SPEQ questionnaires.

Results. Women reported QoL improvement at the 3rd ($P < 0.05$) and at the 6th cycles ($P < 0.01$). By SPEQ, improvement of sexuality during the 3rd and the 6th cycle with respect to baseline experience was observed ($P < 0.05$). The frequency of sexual activity remained basically unchanged (P = NS). Enjoyment and desire improved at the 6th cycle with respect to the 3rd cycle ($P < 0.05$). All women reported decreased dyspareunia at the 3rd and 6th cycles ($P < 0.05$). Interestingly, desire, arousal, orgasm, enjoyment, and sexual activity improved, reaching a peak around the 14th day of the menstrual cycle ($P < 0.05$). At the 3rd and 6th cycle, women on OCs were sexually cyclic, but the peak improvement of desire, arousal, orgasm, enjoyment, and sexual activity appeared around the 7th day of OC intake ($P < 0.05$).

Conclusion. Reduced hormone-free interval is a new concept in low-dose OC regimens. Moreover, the E2V/DNG multiphasic extended regimen has been found to positively modify the sexuality of users. **Caruso S, Agnello C, Romano M, Cianci S, Lo Presti L, Malandrino C, and Cianci A. Preliminary study on the effect of four-phasic estradiol valerate and dienogest (E2V/DNG) oral contraceptive on the quality of sexual life. J Sex Med 2011;8:2841–2850.**

Key Words. Birth Control Pill; Dienogest; Estradiol; Four-Phasic Oral Contraceptive Regimen; Quality of Life; Sexual Behavior

Introduction

Over time, the efficacy and safety of different dosages of ethinyl estradiol (EE) and types of progestins used with OCs have been studied to diminish metabolic alterations and menstrual disorders. Until recently, the estrogen used in OCs has been the stable, highly potent, and biologically active EE. Currently, monophasic mild or low-dose hormonal contraceptives commonly containing 30 μg EE or less, and low doses of synthetic progestogen, are the most

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frequently used in women under 40 years of age [1,2].

The last decade has seen an ever-increasing interest in studying the interaction between hormonal contraceptives and sexual behavior. This has depended on an active realization of new contraceptive formulations and regimens, focusing on reducing the dosage of EE and on developing new progestogens having weak intrinsic androgenic or antiandrogenic properties [3]. Among them, drospirenone (DRSP), a 17α-spironolactone derivate having pharmacological properties which uniquely combine progestogenic and antimineralocorticoid activities, has been developed in combination with EE [4]. This combination provides contraceptive reliability, good cycle control, and widely accepted tolerability. Moreover, it has been shown to have positive effects on both subjective and objective sexual aspects [5–7], as well as on the quality of life (QoL), according to the 21/7 and 24/4 regimens used [8]. Recently, estradiol (E2), the natural estrogen produced by the female gonads, has been introduced into current oral contraception in the form of estradiol valerate (E2V), in combination with a highly potent progestogen, namely dienogest (DNG), a 19-nortestosterone derivate having potent endometrial effect, in a four-phasic formulation (Klaira, Bayer Healthcare Pharmaceuticals, Berlin, Germany). After oral administration, E2V undergoes hydrolysis, becoming E2 during absorption in the gastrointestinal tract [9]. E2V/DNG is administered using an estrogen step-down and a progestin step-up approach over 26 days, having the following hormonal association: E2V 3 mg on days 1 and 2, E2V 2 mg/DNG 2 mg on days 3–7, E2V 2 mg/DNG 3 mg on days 8–24, E2V 1 mg on days 25 and 26, and placebo on days 27 and 28 (Figure 1) [10–12]. The dynamic regimen produces stable levels of E2 over 28 days similar to those observed during the early to mid-follicular phase of a natural cycle [13].

On the basis of recent studies, the preparation is well tolerated and is associated with a high degree of user satisfaction and a low discontinuation rate [14,15]. The current hormonal OCs do not always positively modify the sexual activity of women. In fact, to increase the androgen-binding protein, the endogenous androgen environment changes in the direction of hypoandrogenism [16]. This could provoke decreased sexual desire in OC users, while vaginal dryness could be due to the excessive low EE dosage, with consequent arousal or enjoyment disorder [17]. On the contrary, monophasic OCs containing 3 mg DRSP and 30 μg EE have been shown to have positive effects on both subjective and objective sexual aspects [5].

DNG has no specific affinity for sex hormone binding globulin (SHBG) or cortisol-binding globulin, and does not displace testosterone from SHBG or increase bioavailable testosterone [13,18].

Because the acceptability of a contraceptive depends not only on the side effects but also on the sexual effects [17], we wanted to investigate the QoL and sexual behavior of healthy women on E2V/DNG oral contraceptive.

Materials and Methods

This prospective longitudinal open label study was performed at the Family Planning Centre of the Research Group for Sexology, Department of Maternal and Radiological Science, School of Medicine, University of Catania, Italy. The study protocol was approved by the Institutional Review Board of the Department and conformed to the ethical guidelines of the 1975 Helsinki Declaration. Informed written consent was obtained from each woman before entering the study, and they did not receive any monetary payment. The time of enrollment was from November 2009 to April 2010.

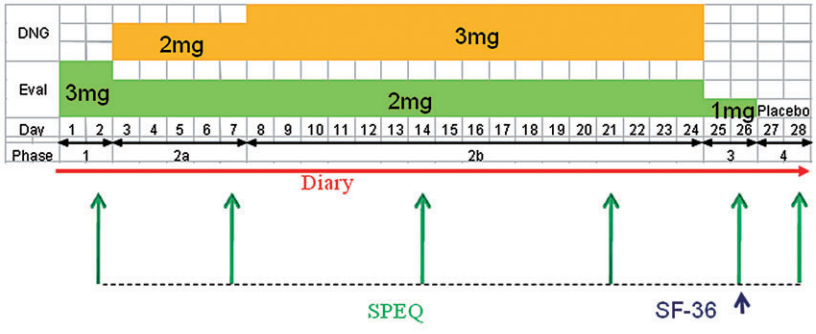

Figure 1 Four-phasic regimen of oral contraceptive containing estradiol valerate and dienogest (DNG), using an estrogen step-down and a progestin step-up approach. Red line shows the days of diary compilation. Green and blue arrows show the days of Short Personal Experience Questionnaire (SPEQ) and Short Form-36 (SF-36) questionnaire administration, respectively.

Subjects and Setting

Women seeking OCs at the Family Planning Centre of the Research Group for Sexology were invited to participate in the study. The sample examined consisted of 72 healthy Caucasian women aged 18 to 48 years, who were sexually active, living with a partner for more than 6 months, and were planning to take OCs for fertility control for at least 1 year. The women were not already using any kind of hormonal contraceptive and showed no contraindications to OC use.

At enrollment, physical and gynecological examinations were performed, and medical, surgical, and medication history were assessed to ensure study eligibility on the basis of inclusion and exclusion criteria. We excluded women with vestibulodynia, current vaginosis, or dystrophic vulvovaginitis. Moreover, women with a history of severe hypertension, thromboembolic disorders, severe diabetes mellitus, obesity (body mass index [BMI] >30 kg/m^2), hepatic dysfunction, hormone-dependent neoplasia, suspicious cervical smear result within the last 6 months prior to start of treatment, pregnancy within the previous 6 months, tobacco use and/or drug abuse, or are breastfeeding, using psychotropic medications, or with a partner having sexual dysfunction were excluded. Inclusion criteria were menstrual cycles with ovulation. To confirm the ovulatory cycle, sonography was performed on days 10, 13, and 16 of the cycle, and serum progesterone concentrations were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available kits (Roche, Monza, Italy). Menstrual cycle was defined as ovulatory when the serum progesterone was >18 IU/mL. Subjects were also given diary cards on which they recorded duration and intensity of menstruation.

Instruments

Each woman underwent a sexual history interview before using the OC and at the 3rd and 6th cycle follow-ups. To define female sexual dysfunction (FSD), the definition and classification of the second report of the international consensus development conference on FSD were used [19].

The Short Form-36 (SF-36) validated questionnaire to assess QoL was used. The questionnaire contains 36 questions grouped into eight categories: physical functioning, physical role functioning, bodily pain, general health, vitality, mental health, social functioning, and emotional role functioning [20]. A visual analog scale (VAS) ranging from *not at all* at the 0-mm mark to *very much/very often* at the 100-mm mark was also used. Women were instructed to place a mark at the point that best corresponded to their feelings. The SF-36 questionnaire was administered at baseline and at the 26th day (the last day of active pill intake) of both the 3rd and 6th cycles of OC intake.

Sexual behavior was assessed using the self-administered Short Personal Experience Questionnaire (SPEQ) [21]. The SPEQ consists of 10 items: five qualitative items, namely female enjoyment, desire, arousal, orgasm, and dyspareunia; and three items investigating the quality of relationship and the sexual performance of the partner, answered on a five-point Likert scale, ranging from 1 (not at all) to 5 (a great deal). By the R-8 item of the SPEQ, it was possible to measure the level of genital pain during intercourse, when present. Therefore, first, dyspareunia was measured at baseline and, consequently, during the 3rd and 6th cycles of OC intake. Finally, two quantitative items on female sexual thoughts and fantasies, and on sexual intercourse during the previous 4 weeks, scored as follows: 0 = never, 1 = less than once a week, 2 = once or twice a week, 3 = several times a week, 4 = once a day, and 5 = several times a day. The SPEQ was used at the 2nd, 7th, 14th, 21st, 26th, and 28th days of the baseline cycle, as well as at the same days of both the 3rd and 6th cycle contraceptive intake. These 6 days of the cycle were chosen on the basis of the changes occurring during a physiological menstrual cycle, and those due to the quantity and association of E2V and DNG. Furthermore, each subject received a diary to record the incidence and characteristics of withdrawal and intracyclic bleeding, premenstrual syndrome (PMS), adverse events, as well as daily sexual activity before and during the E2Val/DNG intake. Sexual activity covers behaviors from self-stimulation to arousal with partner and actual intercourse. Figure 1 shows the timing of questionnaire administration.

Blood samples were obtained from all study participants to measure hormonal levels from day 5 to 8 of the follicular phase. Blood sampling was repeated from day 5 to 8 of the 6th cycle for each woman during the period of OC intake. Serum total testosterone (ng/dL), SHBG (nmol/L), and dehydroepiandrosterone sulfate (DHEAS) (μg/mL) concentrations were measured by ELISA using commercially available kits (Elecsys Systems 2010, Roche). The free androgen index (FAI) was measured by using $FAI = [TT/SHBG\ (\text{nmol/L})]100$.

Statistical Analysis

Using data from previous studies, we set the standard deviation at 2.0, the mean difference at 0.5

between before and after pill use, α (*P* value) = 0.05; therefore, the sample size calculation indicated that 64 subjects would be the minimum number required for the study to have 95% power. Intention-to-treat analyses were performed for all efficacy variables, and included all patients who had undergone the baseline evaluation and had at least one efficacy assessment after the baseline examination. Consequently, we considered the effects of the E2V/DNG used by each woman, with the last observation carried forward for subjects who prematurely discontinued OC use. Statistical analysis was carried out using a software package for Windows 95 (Grantz SA, Primer of Biostatistics; New York: McGraw-Hill, 1997). One-way analysis of variance was used to compare the values obtained at baseline and during the three follow-ups from VAS scales relating to the SF-36 domains. Serum hormone levels were compared longitudinally over time by one-way repeated measures analysis of variance. For comparisons between baseline and follow-up values obtained from the SPEQ items, the nonparametric Wilcoxon rank-sum test with *z* values was used. The results were statistically significant at $P < 0.05$.

Results

Of the 72 women, seven women with both sonography aspects of anovulatory cycles and serum progesterone levels <18 IU/mL were excluded from the study. Moreover, three women refused to take the OC after the baseline evaluation because they changed the objective of their treatment, wanting to include pregnancy, and five were excluded from the study because their relationship finished before starting the OC.

Consequently, 57 Caucasian women in the age range 18–48 years (mean age 28.7 ± 3.3) with menstrual cycle length of 25 to 32 days, duration of menses 5 ± 2.1 days, and with BMI 21.3 ± 3.7 kg/m^2 constituted the sample that underwent clinical and statistical evaluation. Three subjects (5.2%) did not show at the 6th cycle follow-up.

Mild adverse events were recorded in the diary. At baseline, 16 (9.12%) women referred to be affected by PMS, mainly joint, muscle, and back pain, cramps, abdominal pain, breast tenderness, and mild headache. All symptoms of PMS were reduced during the first three cycles of OC intake. Moreover, all subjects reported relief of symptoms at the 6th cycle follow-up. However, adverse events arose during the first three cycles of OC intake; five (8.7%) women had intermenstrual bleeding, five (8.7%) reported nausea, four (7%) had mild headache, and six (10.5%) reported breast tenderness, without provoking discontinuation. Finally, seven (12.2%) and 11 (19.2%) women had hypomenorrhea (3 ± 1.1 days) and amenorrhea, respectively.

Table 1 Serum concentration of SHBG, DHEAS, total testosterone, and FAI calculation in the control cycle and at the 6th cycle of E2Val/DNG usage

Hormone	Baseline	6th cycle	*P*
SHBG (nmol/L)	38 ± 11	57 ± 16	<0.001
DHEAS (μmol/L)	5.7 ± 1.3	5.3 ± 1.4	NS
Total testosterone (nmol/L)	2.1 ± 1.1	1.8 ± 1.2	NS
FAI (%)	5.5 ± 1.3	3.1 ± 1.8	<0.001

DHEAS = dehydroepiandrosterone sulfate; E2V/DNG = estradiol valerate and dienogest; FAI = free androgen index; SHBG = sex hormone binding globulin.

Table 1 shows the serum concentration of SHBG, DHEAS, total testosterone, and FAI calculation observed at baseline and at the 6th cycle of E2V/DNG intake. SHBG increased (66%) during OC intake ($P < 0.001$); contrarily, both DHEAS (–7%) and total testosterone (–14%) decreased, although this was not statistically significant (P = NS). Finally, FAI reduction (–43%) was observed at the 6th cycle follow-up ($P < 0.001$) (Figure 2).

Figure 3 shows the changes of SF-36 scores at the 3rd and 6th cycles of OC intake with respect to baseline values. Women reported QoL improve-

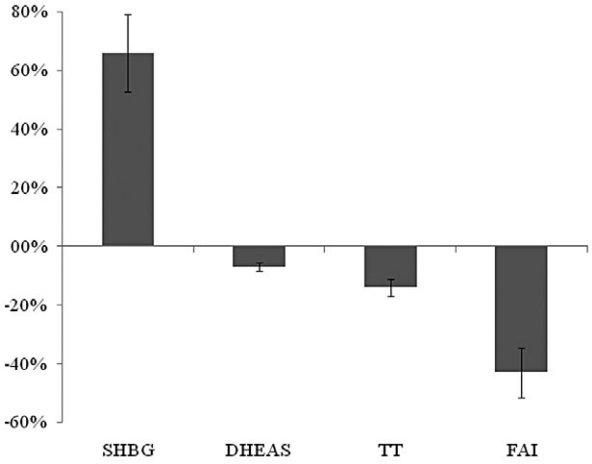

Figure 2 Serum concentration changes of sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), and total testosterone (TT), and free androgen index (FAI) calculation at the 6th cycle of estradiol valerate and dienogest oral contraceptive intake with respect to the baseline values.

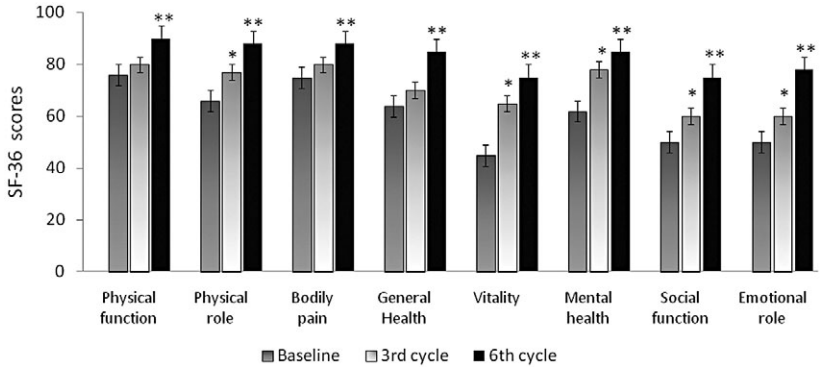

Figure 3 Short Form-36 (SF-36) quality-of-life (QoL) scores in women on four-phasic estradiol valerate and dienogest oral contraceptive intake, compared with baseline values. Subjects reported QoL improvement at the 3rd cycle of pill intake as regards physical role, vitality, social function, and emotional role scales ($P < 0.05$), and at the 6th cycle on all the scales ($P < 0.01$). *3rd cycle versus baseline; **6th cycle versus baseline.

ment at the 3rd cycle on physical role, vitality, social function, and emotional role scales ($P < 0.05$), and at the 6th cycle on all the scales ($P < 0.01$).

Table 2 shows the statistical comparisons by Wilcoxon rank-sum test of the SPEQ scores for each sexual item observed at the 3rd and 6th cycles of women on E2V/DNG OC with respect to the

Table 2 Mean scores of sexual behavior by SPEQ items during four-phasic formulation E2V/DNG oral contraceptive intake, and statistical analyses

			Contraception	
SPEQ (item)	Day of cycle	Baseline N = 57	3rd cycle N = 57	6th cycle N = 53
Enjoyment (1)	2nd	3.2 (±1)	3.8 (±1)*	4 (±0.8)*
	7th	3.3 (±1)	4 (±0.9)*	4.5 (±0.6)*
	14th	3.5 (±0.7)	3.8 (±0.6)*	4.2 (±0.7)**
	21st	3.2 (±0.8)	3.8 (±0.8)*	4 (±0.4)*
	26th	3 (±0.7)	3.7 (±0.6)*	4 (±0.5)**
	28th	2.6 (±0.6)	3.7 (±0.6)*	3.9 (±0.7)*
Arousal (4)	2nd	3.1 (±0.9)	3.6 (±0.9)*	3.7 (±1.1)*
	7th	3.5 (±1.1)	3.9 (±0.9)*	4 (±1.1)*
	14th	3.9 (±0.6)	3.2 (±0.7)*	3.3 (±0.6)*
	21st	2.2 (±0.7)	2.7 (±0.6)*	3 (±0.7)*
	26th	2 (±1.1)	2.5 (±0.9)	2.8 (±1.1)*
	28th	2 (±0.7)	2.5 (±0.9)	2.8 (±0.7)*
Orgasm (5)	2nd	2.9 (±1.4)	3.4 (±1.2)*	3.5 (±1)*
	7th	3 (±1.1)	3.8 (±1.2)*	4 (±1.3)*
	14th	3.5 (±0.6)	3.4 (±0.8)	3.5 (±0.9)
	21st	3 (±0.7)	3.4 (±0.5)*	3.5 (±0.8)*
	26th	2 (±0.7)	3,2 (±0.6)*	3,3 (±0.9)*
	28th	2 (±1.1)	3.2 (±0.5)*	3.2 (±0.8)*
Desire (7a)	2nd	2.1 (±0.8)	2.7 (±1.1)*	2.7 (±1.2)*
	7th	2.8 (±1.1)	3.4 (±0.9)*	3.7 (±0.8)**
	14th	3.7 (±0.6)	3 (±0.5)*	2.9 (±0.7)*
	21st	2.1 (±0.7)	2.5 (±0.5)*	2.6 (±0.8)*
	26th	1.8 (±0.7)	2.2 (±0.4)*	2.4 (±0.5)**
	28th	1.8 (±1.1)	2.2 (±0.4)*	2.4 (±0.4)**
Sexual activity during the last week (7b)	2nd	2.3 (±1.2)	2.4 (±1.3)	2.5 (±1.1)
	7th	2.5 (±0.5)	2.8 (±1.1)	2.9 (±0.9)*
	14th	2.8 (±0.3)	2.2 (±0.6)*	2.3 (±0.5)*
	21st	2.1 (±0.7)	2 (±0.7)	2.1 (±0.5)
	26th	2 (±0.7)	2 (±0.5)	2 (±0.2)
	28th	2 (±1.1)	2 (±0.6)	2 (±0.3)
Dyspareunia (R.8)	2nd	1.6 (±1.1)	0.6 (±0.6)*	0.5 (±0.2)*
	7th	1.2 (±0.2)	0.6 (±0.2)*	0.5 (±0.1)*
	14th	1 (±0.3)	0.9 (±0.3)*	0.6 (±0.1)**
	21st	1.2 (±0.3)	1 (±0.3)*	0.9 (±0.2)*
	26th	1.4 (±0.2)	1 (±0.2)*	0.9 (±0.1)*
	28th	1.4 (±0.3)	1 (±0.3)*	0.8 (±0.2)**

Values are mean ±SD.
Wilcoxon rank-sum test, *$P < 0.05$ vs. baseline; **$P < 0.05$ vs. baseline and 3rd cycle.
E2V/DNG = estradiol valerate and dienogest; SPEQ = Short Personal Experience Questionnaire.

baseline values. It is interesting to note that an improvement was observed for enjoyment, arousal orgasm, and desire during the 3rd and the 6th cycle with respect to baseline experience ($P < 0.05$). The frequency of sexual activity remained basically unchanged ($P = NS$). Each woman had the same, and only one, sexual partner throughout the study period. Items R.1–R.7 and R.10 of the SPEQ reported a good quality of relationship and no difficulties in sexual performance of the partner, respectively. No partner was suffering from sexual dysfunction during the study. Moreover, all women who were affected by dyspareunia before OC intake reported decreased genital pain associated with intercourse at the 3rd and 6th cycles ($P < 0.05$). Finally, enjoyment and desire improved at the 6th cycle with respect to the 3rd cycle ($P < 0.05$).

Figure 4 shows the fluctuation of desire, arousal, orgasm, enjoyment, and sexual activity recorded at baseline and at both the 3rd and 6th cycle of OC intake. From baseline, a progressive improvement of desire, arousal, orgasm, enjoyment, and sexual activity was observed during the postmenstrual and follicular phase (2nd and 7th days), reaching a peak around the 14th day of the cycle ($P < 0.05$). After that, a decrease of SPEQ score was observed during both the luteal and premenstrual phases for each item ($P < 0.05$). At the 3rd and 6th cycle, women on OCs were sexually cyclic, but the peak improvement of desire, arousal, orgasm, enjoyment, and sexual activity appeared around the 7th day of OC intake, gradually decreasing until the 28th day ($P < 0.05$). Moreover, the peak values of sexual activity, desire, and arousal recorded at the 14th day of baseline cycle were similar to those obtained at the 7th day of the 3rd and the 6th cycle of OC intake ($P = NS$). Contrarily, orgasm and enjoyment scores obtained at the 7th day of both the 3rd and 6th cycles of OC

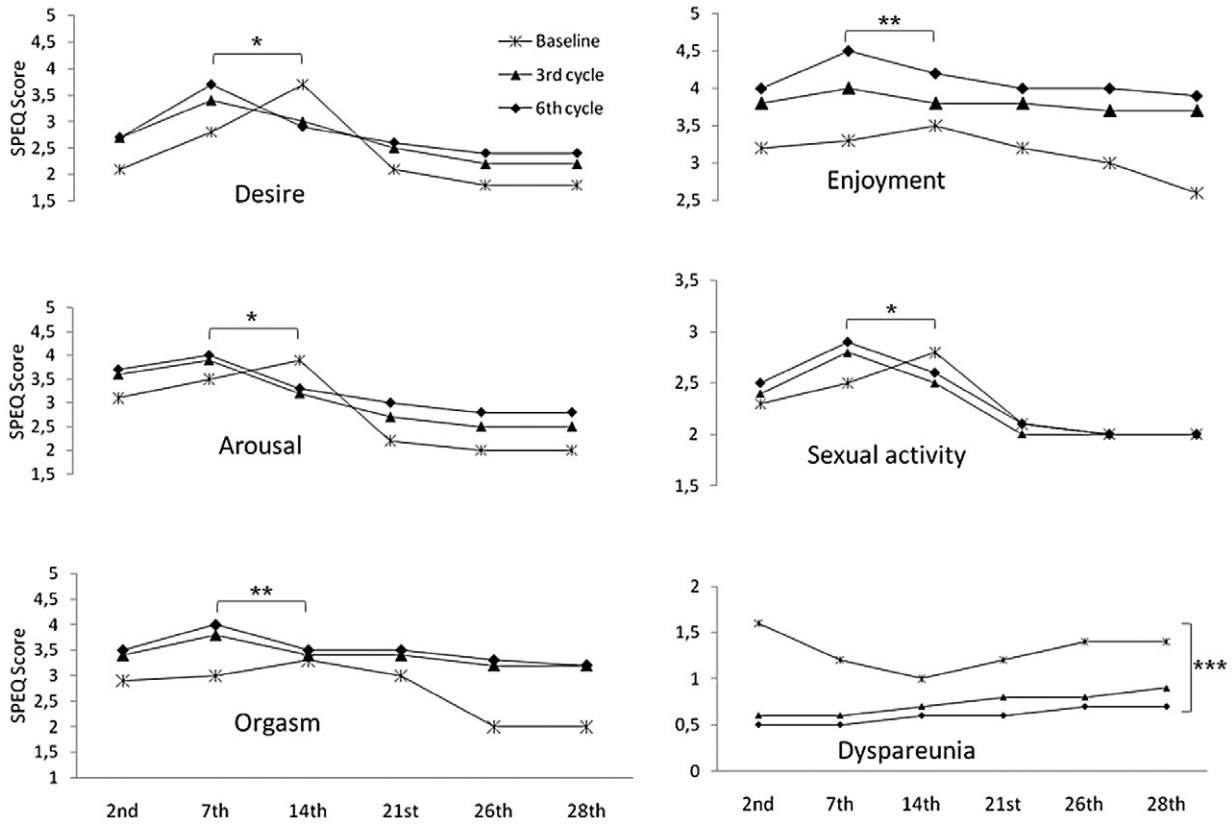

Figure 4 Desire, arousal, orgasm, enjoyment, sexual activity, and dyspareunia changes during the baseline menstrual cycle and at both 3rd and 6th cycle of estradiol valerate and dienogest (E2V/DNG) intake. *The peak values of sexual activity, desire, and arousal recorded at 14th day of baseline were similar to those obtained on the 7th day of the 3rd and the 6th cycle of E2V/DNG intake ($P = NS$). **The peak values of orgasm and enjoyment obtained on the 7th day of both the 3rd and 6th cycles of E2V/DNG intake were higher than those obtained on the 14th day of baseline ($P < 0.05$). ***Diminution of dyspareunia at the 3rd and 6th cycles with respect to baseline ($P < 0.05$).

intake were higher than those obtained at the 14th day of baseline ($P < 0.05$).

Discussion

This was the first study investigating the effect of a new four-phasic OC regimen containing the natural estrogen E2 combined with a 19-nortestosterone derivative DNG (E2V/DNG) on the quality of sexual life. Moreover, E2V/DNG OC has an estrogen step-down and a progestogen step-up sequence, covering 26 days with two placebo tablets making up the 28-day blister [10,12]. The first two tablets have 3 mg E2V to prime the endometrium. The next five tablets contain 2 mg E2V and 2 mg DNG followed by 17 tablets with 2 mg E2V and 3 mg DNG. Finally, there are two tablets with only 1 mg E2V and two placebo tablets. Consequently, the endometrial proliferation and its sensitivity to progestogen, nominally DNG, produce endometrial stroma stability during the middle and the late phase of the cycle [10]. There is normally no estrogen withdrawal during the placebo phase, and this could prevent symptoms due to hormone withdrawal associated with physiological cycles and traditional OC regimens [22]. This depends on the stable E2 levels throughout 28 days, similar to the estrogen values of the follicular phase of a physiological menstrual cycle. E2 is the most potent natural estrogen produced by the female gonads, and has a limited effect on hemostatic parameters with respect to those induced by EE when equivalent potency dosage is considered: in fact, E2V 2 mg is the same as EE 10 μg [23].

Due to the complexity of the methodology used, we performed our study over six cycles of OC intake. To use a longer time, we thought that we could have observed many dropouts; consequently, we would not have had a sufficient number of women to perform a statistical analysis. Usually, six cycles of OC usage are sufficient to make statistical analysis in women on the pill. This is supported by several studies having used a similar number of cycles of treatment [2–8,15,17].

One aspect that our study investigated was the effects of E2V/DNG OC on the QoL by using the SF-36 questionnaire. Women reported improvement of physical role, vitality, mental health, social function, and emotional role scales at the 3rd cycle, and also of physical function, general health, and less bodily pain at the 6th cycle. Women on OCs usually undergo improvement of QoL, the degree and aspects depending on the regimen, compounds, and the duration of usage. Currently, women can use OCs in a subjective, flexible way. The OC regimen is an important aspect to be taken into consideration. The stability reached by extended-cycle OCs with a reduced hormone-free interval might produce positive effects on the quality of sexual life by reducing premenstrual symptoms and reduced bleeding. In our study, the QoL of women on E2V/DNG improved similarly to that obtained from women on the latest extended regimen OCs [8].

The sexuality of women on E2V/DNG OC, evaluated by SPEQ, gradually increased; enjoyment, arousal, orgasm, and desire improved at the 3rd cycle follow-up. Moreover, at the 6th cycle follow-up, enjoyment and desire levels were higher than those obtained at the 3rd cycle. The frequency of sexual activity remained basically unchanged, underlining the fact that often OCs act by increasing the subjective sexual aspects rather than the frequency of sexual activity. This evidence has to serve to demystify the not always correct expectations that women have when they are on OCs. Consequently, counseling should emphasize the changes produced by contraception on the quality of sexual life and not on the quantity of sexual experiences; the latter often depend on the relationship. One of the inclusion criteria of our investigation was that women enrolled in the study had the same, and only one, sexual partner throughout the study period. Moreover, women had a good quality of relationship and their partner was not affected by sexual dysfunction before and during the study. These aspects were investigated by both sexual interview and items R.1–R.7 and R.10 of the SPEQ.

Another interesting aspect revealed by our study is the evident reduction of genital pain associated with intercourse at the 3rd and 6th cycle follow-ups in all women affected by dyspareunia before OC intake. We excluded women with vestibulodynia, current vaginosis, and dystrophic vulvovaginitis [24]. Each of these needs a specific treatment before starting OC. However, if the woman is suffering from dyspareunia during OC use, the pain can be resolved by topical hormonal therapy [25]. In fact, since the OCs are not able to resolve the symptoms, women could have reported data that would have altered the results of our study. On the other hand, we took into consideration the effects of OC on dyspareunia. This symptom could be due to endometriosis, vaginal dryness, and fear of getting pregnant. Moreover, 16 (9.12%) women were affected by PMS, and all

symptoms decreased or improved at the 6th cycle follow-up. This may have acted in improving the QoL and sexual function.

To study the changes of sexual behavior throughout the baseline menstrual cycle, the SPEQ was administrated during postmenstrual, mid-follicular, periovular, luteal, and premenstrual phases. The main event observed was an evident fluctuation of sexual behavior during the menstrual cycle; in fact, a progressive improvement of desire, arousal, orgasm, enjoyment, and sexual activity was observed during the postmenstrual and follicular phase (2nd and 7th days), reaching a peak around the 14th day of the cycle. After that, a decrease of their levels was observed during both the luteal and premenstrual phases. Previously, authors reported similar findings, consisting in a greater sexual interest during the follicular and the periovular phases of the menstrual cycle when more women experience the greatest sexual desire and more erotic fantasies, with respect to the luteal phase [26].

In addition to these, the new result obtained by analyzing the SPEQ scores was that women maintained the cyclic sexual behavior while they were on 28 days of E2V/DNG. Unlike that observed during the spontaneous menstrual cycle, the improvement of desire, arousal, orgasm, enjoyment, and sexual activity reached a peak around the 7th day of OC intake, gradually decreasing until the 28th day. These findings have never been found in previous studies investigating the effects of monophasic and triphasic OCs on sexuality. In fact, the aims of previous studies were focused on the effects of the quality and dosages of steroids on sexuality [5,8,17,27,28], or on the sexual changes during hormonal or nonhormonal contraception using an observational investigation [29]. The only evidence was that women on triphasic OCs could experience greater sexual interest and response than those on monophasics [30].

Another interesting effect due to the pharmacodynamic profile of E2V/DNG is that the serum SHBG concentrations of users increased less than those of women on other OCs, remaining within the normal range [9,13]. SHBG was measured during the follicular phase of the natural menstrual cycle and at the 6th cycle of E2V/DNG OC intake. At the 6th cycle follow-up, the SHBG values increased by 66%. This percentage was less than those obtained with other monophasic or triphasic OCs [31,32]. Moreover, in the same follow-up, a limited DHEAS and total testosterone reduction was observed, –7% and –14%, respectively. Finally, free testosterone, obtained by the FAI, dropped by 43%. The not excessive increase in SHBG could explain the modest reduction in androgen levels and the sexual activity during E2V/DNG intake, especially the level of sexual desire.

The sexual behavior cyclicity of women on E2V/DNG OC could depend on its multiphasic regimen. Similarly to what has been reported during the menstrual cycle, women on E2V/DNG OC did not refer to experiencing a cyclic sexuality explicitly when they were interviewed. This component had been unknown to the women throughout the 28-day OC intake, but it was highlighted, analyzing SPEQ results. By a careful analysis of our data, and given the four variations of steroid association and one placebo phase of the E2V/DNG OC, in our opinion, it would be more correct to begin to consider Klaira a *five-phasic* OC.

The new concept of low-dose OC regimens is based on the reduced hormone-free interval; this kind of regimen has been shown to lower the risk of breakthrough ovulation [33]. Another justification in using extended or continuous administration OCs is to treat endometriosis, dysmenorrhea, and menstruation-associated symptoms that could negatively influence subjective and social aspects [34]. However, the improvement of PMS and/or the changes of mood have been reported during the usual 7-day hormone-free interval rather than during the 21 days of hormone-containing pills of the conventional OC regimen [35], negatively influencing the quality of sexual life of users [36]. New OCs, classified as extended or continuous cycle OCs, will give women the possibility of choosing their contraception, modifying the length of menstrual cycles or alleviating symptoms of coexisting medical conditions, such as endometriosis, dysmenorrhea, and menstruation-associated symptoms [37,38]. The E2V/DNG OC may produce hypomenorrhea and amenorrhea. In our study, they were referred by 12.2% and 19.2% of women, respectively.

However, since our investigation was a prospective longitudinal open label study, it had some limits that will be the objectives of future investigations. In fact, it could be interesting to compare the effects of the multiphasic E2V/DNG OC with a triphasic and/or an extended-cycle OC regimen on the quality of sexual life by a randomized study. Moreover, future methodologies will have to use blinding procedures investigating a large cohort size.

Conclusions

The extended use of OCs could improve the QoL for many women with sexually active lifestyles. E2V/DNG OC, thanks to its extended regimen, has two specific positive effects that have been highlighted by our study, the first is that it maintains cyclic sexuality; the other is that it reduces or eliminates PMS. The first step in prescribing an OC is to understand the needs of the women [27]. Not all monophasic OC users have positive effects on sexuality. It could depend on the inhibition of ovarian steroid cyclicity. Keeping in mind the concept of tailoring an OC, this may be the case of prescribing a multiphasic.

Our study is the first to investigate the effects of a multiphasic OC containing a natural estrogen, namely E2, and the synthetic progestin DNG, on the quality of sexual life. We think that other studies are needed to verify the results obtained by our preliminary study.

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Statement of Authorship

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