ORIGINAL RESEARCH—ENDOCRINOLOGY

Conventional vs. Extended-Cycle Oral Contraceptives on the Quality of Sexual Life: Comparison between Two Regimens Containing 3 mg Drospirenone and 20 μg Ethinyl Estradiol

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ABSTRACT

Introduction. Women may use new oral contraceptives (OC) having flexible extended-cycle regimens with a reduced hormone-free interval.

Aim. To study the changes of the quality of sexual life in users of the traditional 21/7 or extended-cycle 24/4 OC regimens both containing 3 mg drospirenone and 20 μg ethinyl estradiol.

Methods. One hundred fifteen women (age range 18–37 years) were enrolled. Fifty-four women were randomly placed on traditional OC standard regimen, administered for 21 days, followed by a 7-day hormone-free interval (group A); and 61 women were placed on extended-cycle OC regimen covering 24 days of the cycle with a 4-day hormone-free interval (group B).

The Short Form-36 (SF-36) validate questionnaire to assess quality of life (QoL) and the Short Personal Experience Questionnaire (SPEQ) to measure the changes of sexual behavior were administered before starting OC intake and at the 3rd and 6th cycle follow-ups.

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

Results. Group A women reported QoL improvement during the 6th cycle on all the scales ($P < 0.05$). Group B women reported QoL improvement during the 3rd and 6th cycle ($P < 0.05$). Satisfaction with sexual activity, arousal, orgasm, and desire increased during the 3rd cycle in women on the group B ($P < 0.05$). Group A women did not report any change in all SPEQ items. At the 6th cycle, group B women reported better sexual experience than baseline in all SPEQ items ($P < 0.05$). All subjects who were affected by dyspareunia before OC intake reported decreased genital pain associated with intercourse at the 3rd and 6th cycle of both OC regimens ($P < 0.05$).

Conclusion. Women could use OCs in a subjective flexible modality. The extended-cycle OC might produce positive effects on the quality of sexual life, enforcing the concept of tailoring an OC to a woman. **Caruso S, Iraci Sareri M, Agnello C, Romano M, Lo Presti L, Malandrino C, and Cianci A. Conventional versus extended-cycle oral contraceptives on the quality of sexual life: comparison between two regimens containing 3 mg drospirenone and 20 μg ethinyl estradiol. J Sex Med 2011;8:1478–1485.**

Key Words. Drospirenone; Ethinyl Estradiol; Extended-Cycle Oral Contraceptive; Quality of Life; Sexual Behavior

Introduction

The advent of oral contraception, for the first time, separated reproduction from sexuality, emphasizing the importance of the latter. The objective of OCs is to both avoid unwanted pregnancies and to assure the partners a free, balanced, and satisfactory sexual life [1,2]. Today, the acceptability of a contraceptive depends not only on its side effects, but also on the quality of life (QoL)

and sexual changes [3]. However, for many years, the effects of reproductive steroids on sexuality in healthy women were unclear [4,5].

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 ethinyl estradiol (EE), and on developing new progestogens having weak intrinsic androgenic or antiandrogenic properties [6]. In Europe, OCs are the most frequently used hormonal contraceptives in women under 40 years of age, and European physicians prefer modern, monophasic mild, or low-dose hormonal contraceptives commonly containing 30 μg EE or less, and low doses of synthetic progestogen [7,8]; or the more recent sequential multiphasic OCs containing E2 valerate and dienogest. In the past decade, drospirenone (DRSP), a 17α-spironolactone derivate having pharmacological properties, which uniquely combines progestogenic and antimineralocorticoid activities, has been developed in combination with EE [9].

However, 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 [10]. This could provoke decreased sexual desire in OC users, while vaginal dryness could be due to the excessive low estrogenic dosage, with consequent arousal or enjoyment disorder. On the basis of our previous data, low-dose OCs containing 15 μg EE and 60 μg gestodene negatively influenced both subjective and objective measurements of female sexual behavior, each interacting in a cyclic way with the other [3]. 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 [5,11,12]. Moreover combined OCs having 20 μg EE could decrease free testosterone without producing genital discomfort and sexual dysfunction [13]. However, if the woman is suffering from dyspareunia during OC use, the pain can be resolved by topical hormonal therapy [14]. Consequently, 20 μg EE could be the quantity of estrogen below which vulvovaginal pain and dyspareunia arise.

Recently, two pills both containing 3 mg DRSP and 20 μg EE have become part of the OC family, the first having a 21/7 regimen (Yasminelle®, Bayer Schering Pharma AG, Berlin, Germany) [15], the second having a 24/4 regimen (Yaz®, Bayer Schering Pharma AG, Berlin, Germany) [16,17]. Both of them follow the concept of tailoring an OC to a particular woman [18]. While the first is a traditional standard regimen for OCs that is administered for 21 days, followed by a 7-day hormone-free interval, the second is an innovative pill covering 24 days of the cycle with a 4-day hormone-free interval. Each of them may be chosen in prescribing a pill on the basis of menstrual characteristics. DRSP has a minimum half-life of >30 hours, extending its activity for a prolonged time into the shortened hormone-free interval [17]. This pharmacokinetic characteristic of DRSP has been shown to reduce weight gain, bloating, food cravings, breast tenderness, and subjective and somatic symptoms of premenstrual syndrome and premenstrual dysphoric disorder with respect to traditional OC formulations [19].

Due to this characteristic, 3 mgDRSP/20 μEE-24/4 regimen is the only OC with three indications: contraception, the treatment of premenstrual dysphoric disorder in women who wish to use an OC for birth control, and the treatment of moderate acne [20].

The objective of this study was to evaluate the effects of both regimens containing 20 μg EE and 3 mg DRSP on the QoL and on sexual behavior of healthy women.

Materials and Methods

This randomized prospective study was performed at the Family Planning Centre of the Research Group for Sexology, Department of Obstetrics and Gynecology and Radiologic Sciences, 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. Each woman was informed of the hormone content of both OCs, the number of days of pill administration containing the steroids that is 21 or 24 days, and possible changes in the duration and amount of menstrual flow.

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 159 healthy Caucasian women aged 18 to 37 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. Women with a history of severe hypertension, thromboembolic disorder, severe diabetes mellitus, obesity (body mass index > 30 kg/m^2), hepatic dysfunction, hormone-dependent neoplasia, suspicious cervical smear result within the 6 months prior to start of treatment, pregnancy within the previous 6 months, breastfeeding, tobacco use and/or drug abuse, or using psychotropic medications, or 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 immunoassorbent 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.

The women were randomized using numbered, opaque, sealed envelopes containing computer-generated random allocations in a proportion of 1:1 at enrollment evaluation. After enrollment, each woman was placed on one of the two OC regimens, and prescriptions were given.

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 was used [21].

The Short Form-36 (SF-36) validate 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 [22]. A visual analog scale ranging from not at all at the 0 mm mark to very much/very often at the 100 mm mark was used. Women were instructed to place a mark at the point that best corresponded to their feelings. The SF-36 questionnaire was administered before starting OC intake, at the 3rd and 6th cycle follow-ups.

Sexual behavior was assessed using the self-administered Short Personal Experience Questionnaire (SPEQ) [23]. 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); and 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 before starting contraceptive intake, at the 3rd and 6th cycle follow-ups. Furthermore, each subject received a diary to record daily sexual events as well as adverse events before and during the OC intake.

Statistical Analysis

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 thereafter. Consequently, we considered the effects of the OC 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^{TM} (Grantz SA, Primer of Biostatistics, New York, NY, USA: McGraw-Hill, 1997). For comparisons between baseline and follow-up after the 3rd and 6th cycles of the values obtained from the SPEQ items, the nonparametric Wilcoxon rank-sum test with z values was used.

One-way analysis of variance was used to compare the values obtained from the SF-36 domains at baseline and during the two follow-ups.

A two-sided t-test for independent samples by analysis of variance was used to compare the score data between the two groups. The results were statistically significant at $P < 0.05$.

Results

Of the 159 women, 20 refused to take the OC after the baseline evaluation because they changed the objective of their treatment, wanting to include pregnancy, and 15 were excluded from the study for metabolic disorders. Moreover, during enrollment, nine women with both sonography aspects

Table 1 Mean scores and statistical comparison of sexual behavior by SPEQ items between women on 20 μg EE/3 mg DRSP 21/7 regimen (A) and on 20 μg EE/3 mg DRSP 24/4 regimen (B)

SPEQ (item)	Baseline A N = 54 B N = 61	*P**	3 cycle A N = 48 B N = 56	*P**	6 cycle A N = 45 B N = 53	*P**
Enjoyment (1)	A 3.3 (±1)	NS	3.4 (±1)	NS	3.7 (±0.8)	0.4
	B 3.3 (±1.2)		3.6 (±1.1)		4 (±0.7)	
Satisfaction with frequency of sexual activity (2)	A 3.2 (±1)	NS	3.3 (±1)	NS	3.5 (±0.9)	0.04
	B 3.1 (±1.2)		3.5 (±0.8)		3.8 (±0.6)	
Arousal (4)	A 3.4 (±1.2)	NS	3.8 (±0.9)	0.02	3.8 (±1.1)	0.001
	B 3.2 (±1.4)		4.3 (±1.2)		4.5 (±1)	
Orgasm (5)	A 3.2 (± 1.4)	NS	3.4 (±1.2)	NS	3.5 (±1)	0.02
	B 3.2 (±1)		3.6 (±1.1)		3.9 (±0.8)	
Desire (7a)	A 2.4 (±1.3)	NS	2.5 (±1.1)	0.009	2.7 (±1.2)	0.001
	B 2.5 (±1.2)		3 (±0.8)		3.3 (±1.1)	
Sexual activities during the last 2 weeks (7b)	A 1.2 (±1.2)	NS	1.8 (±1.3)	NS	2 (±1.1)	NS
	B 1.3 (±1)		2 (±1)		2.2 (±1.1)	
Dyspareunia (R.8)	A 2.3 (±1.1)	NS	1.7 (±1)	NS	1.4 (±0.6)	0.03
	B 2.2 (±1.2)		1.5 (±0.8)		1.2 (±0.8)	

Values are mean ± SD.
*B regimen vs. A regimen *P* values.

of anovulatory cycles and serum progesterone levels < 18 IU/mL were excluded from the study.

Consequently, 115 Caucasian women in the age range 18–37 years (mean age 25.7 ± 3.1) with menstrual cycle length of 24 to 35 days, duration of menses 5 ± 1.3 days, and with body mass index (BMI) 24.6 ± 2.3 kg/m^2 constituted the sample undergoing clinical and statistical evaluation. Of these, 54 women were randomly placed on DRSP 3 mg/EE 20 mcg 21/7 (group A) and 61 women on DRSP 3 mg/EE 20 mcg 24/4 (group B) regimens.

Both groups were similar with respect to age (A, 24.8 ± 4.5; B, 25.9 ± 3.9), menstrual cycle length (A, 25 to 34 days; B, 24 to 35 days), duration of menses (A, 4 ± 1.9; B, 5 ± 2), and BMI (A, 24.3 ± 2.8; B, 24.7 ± 1.1).

Of group A, four women (7.4%) discontinued the OC during the 3rd cycle and three (5.5%) discontinued during the 4th cycle, due to problems related to bleeding or spotting; and two (3.9%) discontinued due to headache during the 3rd cycle. On the other hand, two (3.2%) and three (4.9%) women of group B discontinued due to nausea during the 2nd and 3rd cycles, respectively, and three subjects (4.9%) did not show at the second follow-up.

Moreover, mild adverse events arose during OC intake, nominally intermenstrual bleeding (5 in group A and 3 in group B), nausea (4 in group A and 3 in group B), mild headache (4 in group A and 2 in group B), breast tenderness (5 in group A and 3 in group B), without provoking discontinuation.

The SPEQ detected changes in sexuality allowing assessment of OC effect on sexual desire, sexual arousal, orgasm and sexual enjoyment, and on satisfaction with the current frequency of sexual activity, frequency of sexual activities during the previous 2 weeks, and frequency of experiencing pain during intercourse. Sexual activity covers behaviors from self-stimulation to arousal with partner and actual intercourse. 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.

Table 1 shows the sexual changes during both the OC regimens, and the statistical comparison of sexual behaviors obtained by SPEQ between groups A and B. At the 3rd cycle follow-up, a statistically significant difference was observed for desire ($P < 0.009$) and arousal ($P < 0.02$) comparing the two OC regimens. At the 6th cycle follow-up, a statistically significant difference was obtained for enjoyment, desire, arousal, orgasm, satisfaction with frequency of sexual activity, and sexual pain during intercourse when scores from the two groups were compared ($P \leq 0.04$). Over the study period, there was no difference between the two groups comparing the item for sexual activity (P = NS). Finally, sexual pain decreased in group B more than in group A at the 6th cycle follow-up ($P < 0.03$).

Table 2 shows the statistical comparisons of the Wilcoxon's rank-sum of the SPEQ scores for each sexual item observed at the 3rd and 6th cycles of both OC regimens with respect to the baseline values.

Firstly, satisfaction with sexual activity ($P < 0.05$), arousal ($P < 0.001$), orgasm ($P < 0.05$), and desire ($P < 0.01$) increased at the 3rd cycle in

Table 2 Statistical comparisons of sexual behavior by SPEQ items of women on 20 μg EE/3 mg DRSP 21/7 regimen (A) and on 20 μg EE/3 mg DRSP 24/4 regimen (B) observed at follow-ups with respect to the baseline values

			3rd cycle vs. baseline				6th cycle vs. baseline	
PEQ Items	W	τ_i	Z_W	*P*	W	τ_i	Z_W	*P*
Enjoyment	A 92	38	—	NS	225	29	3,342	<0.02
	B 58	28	—	NS	324	32	4,452	<0.001
Satisfaction with sexual activity	A 32	34	—	NS	132	22	1,244	<0.05
	B 298	21	3,743	<0.05	351	26	4,578	<0.001
Arousal	A 34	24	—	NS	164	30	2,446	<0.05
	B 315	19	3,554	<0.001	356	24	4,694	<0.001
Orgasm	A 41	25	—	NS	68	21	—	NS
	B 182	32	2,980	<0.05	339	30	4,281	<0.001
Desire	A 32	34	—	NS	84	28	—	NS
	B 115	38	1,214	<0.01	232	28	3,720	<0.001
Sexual activity during the last 2 weeks	A 34	37	—	NS	182	30	2,950	<0.05
	B 33	34	—	NS	275	26	3,212	<0.05
Dyspareunia	A –156	25	–2,338	<0.01	–132	23	–2,023	<0.05
	B –227	23	–3,228	<0.001	–296	21	–3,712	<0.001

W = rank sum; τ_i = overriding rank number; Z_W = statistical Wilcoxon test.

women on the OC 24/4 regimen than at baseline. Women on the OC 21/7 regimen did not report any change in all SPEQ items (*P* = NS).

Secondly, at the 6th cycle women on the OC 24/4 regimen reported better sexual experience than baseline in all SPEQ items ($P < 0.05$). On the contrary, women on the OC 21/7 regimen had improvement in sexual enjoyment ($P < 0.02$), satisfaction with sexual activity ($P < 0.05$), arousal ($P < 0.05$), and frequency of sexual activity ($P < 0.05$), but not in desire and orgasm experience (*P* = NS).

It is interesting to note that all women who were affected by dyspareunia before OC intake reported decreased genital pain associated with intercourse at the 3rd and 6th cycle of both OC regimens ($P < 0.05$).

Figure 1 shows the changes of SF-36 scores in group A and group B at the 3rd and 6th cycles of OC intake with respect to baseline values. Women on the OC 21/7 regimen reported QoL improvement at the 6th cycle on all the scales ($P < 0.05$). No significant differences were observed between baseline and the 3rd cycle of OC intake values (*P* = NS). Contrarily, women on the OC 24/4 regimen reported QoL improvement at the 3rd cycle for physical function, physical role function, general health, vitality, mental health, social function and emotional role function, and an improvement on each scale during the 6th cycle.

Discussion

This prospective study compared the changes of the quality of sexual life of two groups of women using traditional 21/7 or extended 24/4 OC regimens both containing 3 mg DRSP and 20 μg EE. The first event observed was that at the 3rd cycle women on the 24/4 regimen pill experienced an improved sexual life than those on the 21/7 regimen pill, mainly for desire, arousal and orgasm experience, and for decreased dyspareunia. Moreover, even if sexual experience increased during the 6th cycle of both groups, women on the 21/7 regimen pill reported values of desire and orgasm similar to those referred at baseline. Finally, the QoL was reported to be better than at baseline from women on the 24/4 regimen pill during the 3rd cycle. On the contrary, women on the 21/7 regimen pill experienced QoL improvement at the 6th cycle.

Except for the early biphasic and triphasic pills, the regimen of monophasic OCs is mainly constituted by 21 active pill days containing both estrogen and progestogen steroids, and a 7-day hormone-free interval. The design of this type of pill was thought to give women a monthly pseudomenstrual withdrawal with bleeding similar to that of the physiologic cycle. The first pills containing 30 mg DSPR, namely Yasmine and Yasminelle, were both based on the 21/7 regimen. Their difference was in the quantity of EE, 30 μg and 20 μg, respectively. Currently, a new concept of low-dose OC regimens is arising based on the reduced hormone-free interval; this kind of regimen has been shown to reduce the risk of breakthrough ovulation [24]. Another justification in using extended or continuous administration OCs is to treat endometriosis, dysmenorrhea, and menstruation-associated symptoms that could influence negatively subjective and social aspects [25].

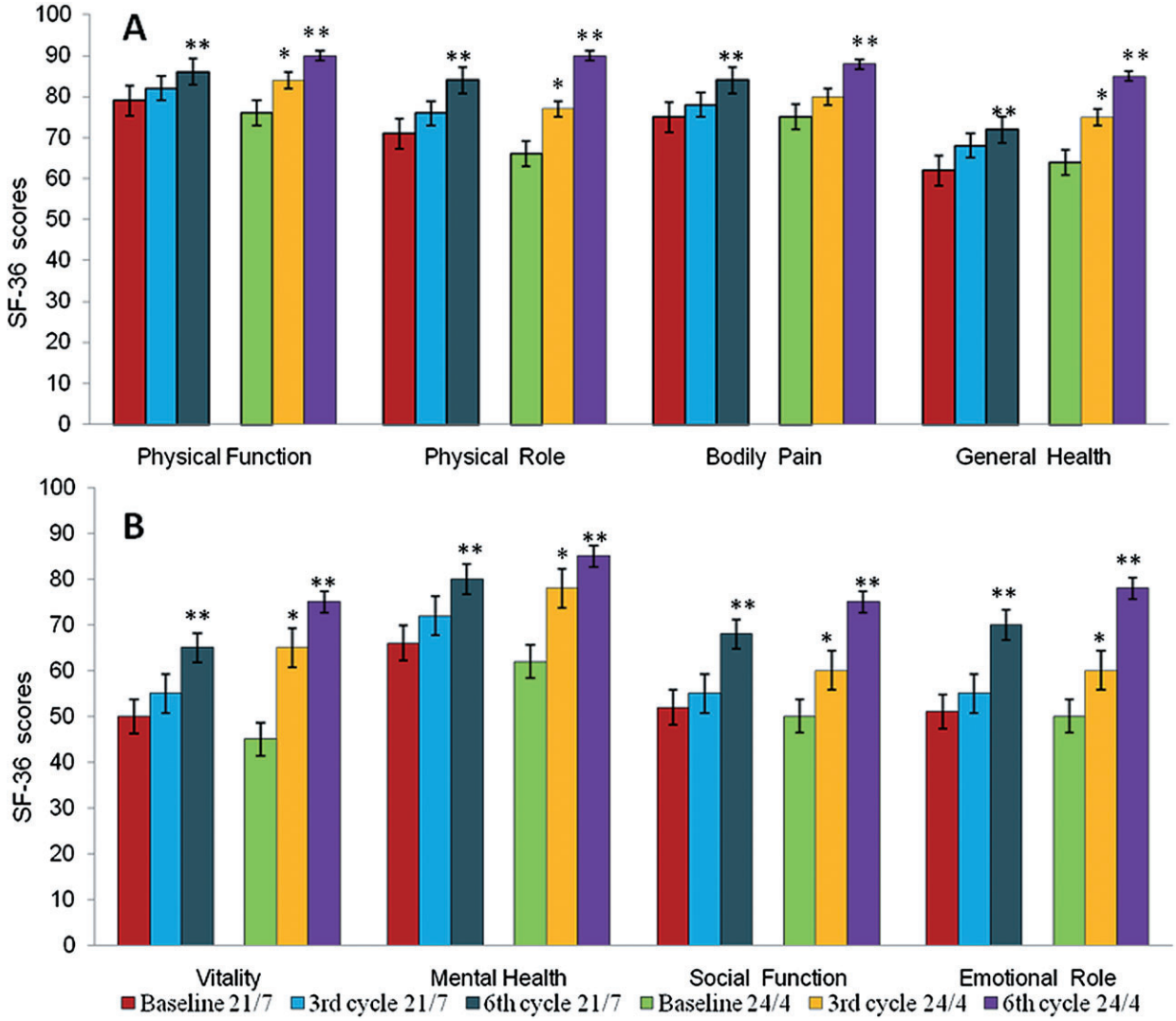

Figure 1 SF-36 QoL scores from women on 21/7 or 24/4 20 g EE/3 mg DRSP OC regimens. Subjects on the 21/7 regimen reported QoL improvements at the 6th cycle of pill intake on all the scales ($P < 0.05$) but not at the 3rd cycle (P = NS; A–B). Subjects on the 24/4 regimen reported QoL improvement at the 3rd cycle of pill intake for physical function, physical role function, general health (A), vitality, mental health, social function, and emotional role function (B); and at the 6th cycle of pill intake for each scale (A–B). *3rd cycle vs. baseline; **6th cycle vs. baseline.

Interestingly, in the hormonal contraception field, there has been the development of new progestagens having no intrinsic androgenic properties and antiandrogenic activity. To increase the androgen-binding protein, the endogenous androgen environment changes in the direction of hypoandrogenism [10], even if the free testosterone reduction usually depends on EE, the quantity of which is able to vary the level of the sexual hormone-binding globuline [26].

During the follicular phase of the menstrual cycle, women usually report a greater sexual interest, persisting during the periovular phase, when more of them experience the greatest sexual desire and more erotic fantasies, with respect to the luteal phase [27,28]. Due to pill use, this important cyclic aspect of sexual behavior could become noncyclic. DRSP, even if having antiandrogenic properties, has been shown to have no negative activity on the sexual behavior of women [5]. Moreover, the antimineralcorticoid activity of DRSP could result in special benefits in avoiding estrogen-related fluid retention, improving compliance of women taking OCs [29]. However, other events could arise during OC usage such as insufficient control of the premenstrual syndrome and mood changes negatively influencing the quality of sexual life of users [30]. The improvement of premenstrual syndrome

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 [31].

The explanation about these adverse events and counseling could likely result in greater satisfaction and therefore may increase the likelihood that a woman may choose to stay on the pill [32]. On the other hand, physicians need training to improve their knowledge on contraception to be able to help each patient choose a contraceptive that could be appropriated for her based on her medical history and preferences for kind of contraceptive [33].

Apart from the innovative 24/4 OC regimen, which we have used in this study, women could use the same pill in a subjective flexible modality decreasing the frequency of menses to four times yearly or less. New OCs, classified as extended or continuous cycle OCs, will give women the possibility to choose their contraception modifying the length of menstrual cycles or alleviating symptoms of coexisting medical conditions, such as endometriosis, dysmenorrhea, and menstruation-associated symptoms [34,35]. The continuous use of OCs will be able to improve the QoL for many women with sexually active lifestyles [36].

However, our study had some limits that will be the objectives of future research. In fact, we did not consider the basal hormone levels of both groups that could influence the sexual function during the OC intake. Moreover, future methodology will have to use blinding procedures investigating a large cohort size.

Conclusions

The flexibility of OC use may act positively on the menstrual cycle of women with medical disorders, producing positive effects on the quality of sexual life. Moreover, due to specific metabolic activities of DRSP and to a better modulation of premenstrual symptoms of the 24/4 regimen pill, the tonic phase of all the menses is able to produce an improved quality of health. We have to emphasize the concept that all women are different, and we are going into an era where the concept of tailoring an OC to a particular woman has to be adopted. Thus, the first step in prescribing an OC is to understand the needs of the subject [37].

In the near future, studies investigating the effects of "long administration pills" will be needed, to analyze and understand in what way the QoL could change.

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Statement of Authorship

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