Change to Either a Nonandrogenic or Androgenic Progestin-Containing Oral Contraceptive Preparation is Associated with Improved Sexual Function in Women with Oral Contraceptive-Associated Sexual Dysfunction

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ABSTRACT

Introduction. It is a commonly held belief that combined oral contraceptive (COC) pills containing an androgenic progestin may be less likely to impair sexual function than COCs containing an anti-androgenic progestin.

Aim. The study aims to compare the effects of a COC containing a progestin with an anti-androgenic profile (estradiol valerate [E_2V]/dienogest [DNG]) to that of one with an androgenic progestin (ethinyl estradiol [EE]/levonorgestrel [LNG]) on sexual function in women with COC-associated sexual dysfunction.

Methods. In this multicenter, randomized, double-blind, noninferiority study, women with COC-associated female sexual dysfunction (FSD) were randomized to E_2V/DNG or EE/LNG for six cycles. The primary outcome was the change in the sum of Female Sexual Function Index (FSFI) desire and arousal component scores between baseline and cycle 6. Secondary outcome measures included changes to the FSFI domains, the Female Sexual Distress Scale (FSDS-R), Vaginal Health Assessment, the Atrophy Symptom Questionnaire, and the Psychological General Well Being Index over six treatment cycles.

Main Outcome Measure. The main outcome is the change in the sum of FSFI desire and arousal component scores between baseline and cycle 6.

Results. Of 276 women screened, 213 received treatment and 191 completed the study. The mean increase in the sum of FSFI desire and arousal component scores was 5.90 (standard deviation [SD] 5.45) for E_2V/DNG and 5.79 (SD 6.17) for EE/LNG (change from baseline $P < 0.0001$, both groups). Both treatments showed equal efficacy and were associated with improvements in all domains of the FSFI, with no between-group differences. Both COCs reduced the distress associated with FSD, as indicated by reduced FSDS-R scores.

Conclusion. In women with COC-associated FSD, switching to either E_2V/DNG or EE/LNG was associated with equivalent improvements in symptoms, challenging the perception that COCs containing anti-androgenic progestins have a detrimental effect on sexual function relative to those containing androgenic progestins. **Davis SR, Bitzer J, Giraldi A, Palacios S, Parke S, Serrani M, Mellinger U, and Nappi RE. Change to either a nonandrogenic or androgenic progestin-containing oral contraceptive preparation is associated with improved sexual function in women with oral contraceptive-associated sexual dysfunction. J Sex Med 2013;10:3069–3079.**

Key Words. Dienogest; Estradiol Valerate; Ethinyl Estradiol; Oral Contraception; Female Sexual Dysfunction

Clinical trial registration number: NCT00764881
Clinical trial registry: http://www.clinicaltrials.gov

Introduction

The use of combined oral contraceptives (COCs) has been associated with untoward effects on sexual function, particularly desire and arousal [1,2]. Sexual side effects are recognized as reasons women may discontinue or switch contraceptive pills [3,4]. Testosterone is believed to play an important role in sexual desire, and transdermal testosterone has been found to increase sexual desire in premenopausal women for whom this was previously diminished [5]. The anti-gonadotropic effect of COCs results in suppression of ovarian androgen production, whereas the estrogen component increases the production of sex hormone-binding globulin (SHBG) [6]. The combined effects result in decreased levels of total and free testosterone [6]. This iatrogenic testosterone deficiency is believed to underpin the adverse effects of COCs on sexual function [7–9], although there is no specific level of testosterone below which female sexual dysfunction (FSD) is more likely to occur [9,10]. COCs containing higher doses of ethinyl estradiol (EE) are associated with greater increases in SHBG and, hence, lower free testosterone [11]. Thus, it is plausible that COCs containing lower doses of EE or less potent estrogens, such as estradiol, might be less likely to lower free testosterone levels and affect sexual function [12].

As progestins exhibit varying androgenic potency, those exhibiting stronger androgenicity, such as levonorgestrel (LNG) [13,14], might be a better option for women experiencing diminished sexual well-being associated with COC use. Hence, it is not uncommon for women experiencing COC-associated diminished sexual desire and/or arousal to be switched to a COC containing LNG [14]. However, evidence that more androgenic progestins are less likely to be associated with FSD than anti-androgenic progestins is lacking.

To fully understand the role of COCs in FSD, one must also consider their effect on vaginal health. The administration of exogenous estrogen, as in hormone replacement therapy or via the contraceptive pill, can increase levels of SHBG and, consequently, decrease levels of testosterone, the effect of which can contribute to vaginal atrophy [15,16]. In addition, COCs containing low doses (<20 μg) of EE have been associated with decreased vaginal lubrication and vulvar vestibulitis [17,18]. The precise role of COC androgenicity, and the effect of estradiol valerate (E_2V) relative to EE in terms of affecting vaginal health, remain to be determined and constitute points of interest for this study.

Although one approach for the management of women with COC-associated sexual dysfunction is discontinuation of hormonal contraception [19], for many women this is not an acceptable option. We have undertaken this study to investigate the effects of a COC containing E_2V and the anti-androgenic progestin, dienogest (DNG) [20], and one containing EE and the androgenic progestin LNG, on sexual desire, arousal, and other parameters of sexual health in women experiencing COC-associated sexual dysfunction.

Methods

Study Participants

Women from 32 centers in Australia, Austria, Belgium, Germany, Italy, Spain, and Thailand participated between January 2009 and July 2010. Eligible participants were between 18 and 50 years of age (maximum age of 30 years if a smoker) and, at screening, were taking the COC that they perceived had reduced their sexual desire, with effects for at least 3 months but not longer than 1 year. Eligible participants also had to be willing to continue COC use and switch to E_2V/DNG or EE/LNG.

At screening, women were required to have a total score of ≤18 for the desire and arousal components (defined as the sum score of questions 1 to 6) of the Female Sexual Function Index (FSFI) [21]. It was not possible to identify an appropriate threshold for combined scores of desire and arousal from the literature; therefore, taking into account the overall score, as well as the score relevant for inclusion, it was assumed that a difference of ≤5 would adequately demonstrate that there is no clinically meaningful difference between the treatment groups. Of the women who were screened, 28 women in the E_2V/DNG treatment group, and 20 women in the EE/LNG group, had been taking an LNG-containing COC prior to switching over to study treatment, while five women in the E_2V/DNG group and four in the EE/LNG group had been taking COCs containing DNG.

Women also had to be in a sexual relationship with a competent sexual partner and have a normal or clinically insignificant Pap smear in the preceding 6 months. Women were excluded from the study if they had a sexual aversion/phobic disorder, or sexual pain disorder/dyspareunia. Other