

Effects of Sex Hormones in Combined oral Contraceptives and Cyclofem on Female Sexual Dysfunction Score: A Study on Iranian Females

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Abstract

Introduction: Unwanted pregnancy can endanger reproductive health, and its complications could adversely affect quality of life in females, families, and the community. A large number of unwanted pregnancies are terminated with abortion or stillbirth. Sex is an important aspect of quality of life. According to reproductive rights, females have the right to experience a safe and enjoyable sexual relationship. This study aimed at comparing sexual function scores between females taking combined oral contraceptives and Cyclofem at health centers affiliated to Shahid Beheshti University of Medical Sciences of Tehran, Iran, During Year 2013.

Methods: This descriptive-comparative study was carried -out on 240 females (each group 120) in Tehran, Iran, by multistage sampling. Data collection tools had 3 parts; General Health Questionnaire (GHQ), demographic variables, and Female Sexual Function Index (FSFI) that were completed by interviews. Descriptive statistics, independent t, Mann-Whitney test, chi-square, and SPSS16 were used for analysis of data. P-values less than 0.05 were considered statistically significant.

Results: The difference in sexual function between combined oral contraceptives and cyclofem was insignificant. Scores of desire and arousal dimensions were better in combined oral contraceptive consumers than cyclofem users.

Conclusions: It is important for females to choose hormonal contraception methods, which are the most effective, yet, cause the least sexual dysfunction.

INTRODUCTION

Annually, 46 million out of 87 million unwanted pregnancies (more than 50%) do not result in live birth around the world. In 2008, 38 million abortions took place worldwide. According to the World Health Organization (WHO), one in every 10 pregnancies lead to unsafe abortion, and one in every 8 unsafe abortion leads to mother's death. This incident occurs 6 times more in developing countries [1]. According to studies from Iran, one-third of pregnancies is unintended [2]. The risk of unintended pregnancies is less in

females, who use hormonal methods of contraception [3]. Having high effectiveness, contraceptive methods are considered desirable because they are easy to use and do not interfere with intercourse [4]. In summary, access to highly effective reversible contraception offers a way to potentially decrease the incidence of unintended and mistimed pregnancies. The principle aim of family planning is to prevent unwanted pregnancies. Cyclofem is a type of combination injectable hormonal contraceptive. Cyclofem contains 0.5

ml of active ingredients, comprised of 25 mg of medroxyprogesterone acetate and 5 mg of estradiol cypionate, and is injected on a monthly basis [5]. The efficacy of this method is 99.8% in the first year [6]. In 70 000 females per year, only 6 cases of failure were reported. This rate of efficacy is similar to that of sterilization in females. After discontinuation of the use of this product, return to fertility occurs much faster than progestin injection [7]. Only cyclofem has been introduced in Iran's family planning program. Estradiol in cyclofem is intermediate acting, and maintains the highest plasma level for approximately 15 days, and is reduced 3 weeks after administration, which presents as uterine bleeding. Cyclofem is an effective contraceptive method, with 0 to 0.2 cases of pregnancy in 100 females per year [8]. Combined Oral Contraceptives (COC) are safe and effective options for preventing pregnancy. Combined Oral Contraceptives are considered the most commonly used and popular contraceptive. Proper use of COC provides almost absolute protection against pregnancy [9]. Sex hormones, such as estrogen and progesterone, could impose different effects on female's sexual behaviors and functions through vaginal tissue and the central nervous system [10]. Studies have indicated that hormones used in contraceptive methods have effects on sexual function of females in reproductive ages [11]. Females using hormonal contraceptive methods have experienced positive, negative or no effects on their libido [6]. Prevalence of sexual dysfunction was 48.3% in Turkey, 22% in Chile and 49% in Brazil [12-14]. In Iran, sexual dysfunctions have a wide range from 8.5% [15] to 19.2% [16] and 31.5% [17]. Ramezani Tehrani et al. (2014) reported the prevalence of sexual dysfunction as 27.3%, while frequency of desire, arousal, lubrication, and orgasmic disorders, were 18.6%, 39.9%, 18.9%, and 27.3%, respectively. They reported the 56.1% of females had dyspareunia and 15.2% were dissatisfied with their sexual life [18]. This problem is so important that it accounts for 88% of divorces [19].

One of the major side effects of hormonal contraception methods is their effect on sexuality and libido, which are one of the main reasons for discontinuation in females, who used hormonal contraception [20]. A satisfaction with contraceptives depends upon lifestyle, side effects, and concern about the likelihood of pregnancy. Satisfactory sexual relationship increases satisfaction with life [4]. The current study aimed at determining whether cyclofem and COC effect sexual function and its aspects. There are effective methods for regulating fertility, yet, none is without complications [21]. In choosing contraceptive methods, females are faced with many challenges, including benefits and side-effects [22]. Lack of early and adequate training about sexual matters is a major concern for females of any age. The current study aimed at comparing the scores of sexual function of females using cyclofem with those using COC, attending the health centers affiliated to Shahid Beheshti University of Medical Sciences in Tehran, Iran, during year 2013.

METHODS

This descriptive comparative study was conducted from May to November 2013 with multistage sampling, includ-

ing 240 Iranian females, who lived in Tehran and referred to health care centers. The area of health care centers affiliated to Shahid Beheshti University of Medical Sciences in Tehran was divided to 4 zones, namely North, South, West, and East, and then 2 centers were randomly selected from each region. The Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran (Iran) approved this study. During sampling, participation in this study was voluntarily, and subjects could decline to continue at any stage of the study. The researcher introduced herself and explained the objectives of the study to the participants. Participants were assured of the confidentiality of their information. They were recruited according to the inclusion criteria. Study inclusion criteria were Iranian nationality, minimum of 3 months of use of contraceptive methods, no lactation, no addiction, psychological disorders or use of antidepressants in the any of the spouses, lack of adverse life event in the females over the 6 months prior to the study.

In this study, 264 females were registered. Because of the impact of depression and anxiety on sexual function, the 28-item Persian version General Health Questionnaire (GHQ-28) was first completed for assessment mental health. The GHQ has been used in previous studies [23, 24], and is scored on a Likert scale (not at all = 0, about normal = 1, more than normal = 2, and much more than normal = 3). It had 4 subscales, including somatic symptoms (7 questions), anxiety and sleep disorder (7 questions), social function (7 questions), and depression symptoms (7 questions). Subjects with a score of 22 marks or more were excluded. Based on the test results, 18 samples were excluded from the study (scores \geq 22). In the cyclofem group, there were 123 participants, yet 3 were excluded (not meeting = 1 and lactation = 2). In the COC group, there were 133 participants, yet 13 were excluded (not meeting = 8 and using antidepressants by the female = 5), so 240 subjects were divided to 2 equal groups of 120 each.

Cyclofem ampoule (manufactured by Iran Hormone Tehran, Iran) contains 25 mg of medroxyprogesterone acetate and 5 mg of estradiol cypionate, and was injected at monthly intervals, and COC (Aburailhan pharmaceutical Co, Tehran, Iran), containing 0.15 mg of levonorgestrel and 0.03 mg of ethinyle estradiol, was continuously administered at 3-week intervals at health centers. The data collection tool was completed by the researchers through interviews. Next, questions about demographic variables with 33 questions were filled out. Finally, the Female Sexual Function Index (FSFI) questionnaire that has been used in various studies, was completed [25, 26]. This questionnaire contained 19 questions with 6 options, with 2 questions on sexual desire, 4 on arousal, 4 on vaginal lubrication, 3 on orgasm, 3 on pain, and 3 on sexual satisfaction, designed with a Likert scale, and assesses sexual function over the past 4 weeks. Total score is obtained from the sum of 6 domain scores and ranges from 1.2 to 36. Maximum score was 36, and scores less than 28 indicated unfavorable sexual functions. In each area, the score range was 0 to 6. Content validity was used to ascertain validity of the questionnaire, and internal consistency was ensured using Cronbach's alpha coefficient ($\alpha = 0.81$). For reliability, re-test was used with a 10-day interval ($r = 0.83$). Data were

analyzed with Statistical Package Software for Social Science, version 16 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, independent *t*, Mann-Whitney test, and Chi-square, were used. An alpha level of less than 0.05 was accepted in all tests as statistically significant.

RESULTS

This study was conducted on 240 females, and their demographic details are presented in Table 1. All participants were Muslim. Sexual function in females using cyclofem was favorite (65.8%) compared to those using COC (73.3%). The

FSFI scores for each group are shown in Table 2. The difference in total sexual function scores between cyclofem and COC groups was not significant (mean score of total sexual function in the COC group was 29.15 ± 6.13 versus 29.53 ± 4.23 in the cyclofem group), however, in terms of sexual desire and sexual arousal, the cyclofem group obtained lower scores than the COC group (mean score of desire domain in the COC group was 3.85 ± 1.31 versus 3.40 ± 0.78 in the cyclofem group; mean score of arousal domain in the COC group was 4.51 ± 1.39 versus 4.16 ± 0.86 in the cyclofem group. Comparison of sexual function in COC and Cyclofem users is indicated in Table 2 (P < 0.05).

Table 1: Distribution of the Demographic Characteristics of Females Consuming Combined Oral Contraceptives and Cyclofem

Variable	COC (n = 120)	Cyclofem (n = 120)	Test	P Value
Age, y(SD)	29.58(5.42)	28.26(5.08)	Independent T	NS
Age of marriage,y(SD)	19.92(3.98)	18.55(3.62)	Independent T	NS
Duration of marriage, y(SD)	9.57(5.94)	8.70(4.89)	Independent T	NS
Age of first conception, y(SD)	20.73(6.31)	21.12(4.84)	Independent T	NS
Gravidity(SD)	1.82(0.22)	2.15(1.22)	Independent T	NS
Duration of use, m(SD)	50.58(7.13)	50.32(7.83)	Independent T	NS
Menstruation status, No. (%)				
Regular	107(89.2)	102(85)		
Irregular	10(8.3)	17(14.2)	Chi-square	NS
Amenorrhea	3(2.5)	1(0.8)		
Side effect, No. (%)				
No	105(87.5)	101(84.2)	Chi-square	NS
Yes	15(12.5)	19(15.8)		
Education, No. (%)				
Illiterate	3(2.5)	2(1.7)		
Primary school	18(15)	12(10)		
Secondary school	20(16.7)	28(23.3)	Chi-square	NS
High school	67(55.8)	72(60)		
Above	10(12)	6(5)		

Table 2: Comparison of Sexual Function in Combined Oral Contraceptives Consumers and Cyclofem Users

Domain	COC (n = 120)	Cyclofem (n = 120)	P Value
*Desire	(3.80-5.6)4.21	(3.00-4.8)3.60	0.001a
*Arousal	(4.1-5.8)5.10	(3.6-4.8)4.20	0.020a
*Lubrication	(4.5-5.8)5.10	(4.5-6.0)5.25	0.116a
*Orgasm	(4.2-6.0)5.10	(4.0-6.0)4.80	0.296a
*Pain	(5.8-5.9)5.50	(5.2-6.0)6.00	0.246a
*Satisfaction	(4.1-6.0)4.90	(3.6-6.0)4.80	0.812a
**Total	(6.13)29.15	(4.23)29.53	0.102b

* U test* Median (IQR)

**M ± SD

a: Mann-Whitney test

b:Independent t-test

DISCUSSION

The effect of hormonal contraception on sexual function in users of contraceptives has been far less frequently studied. However, in the current study, the relationship between COC and Cyclofem and sexual function in females was insignificant. The authors did not find any study about this relationship yet the World Health Organization (WHO) (2007) and Lande and Richey (2006) reported no sufficient evidence that the use of combined injectable hormonal therapy changes female's sexual function [27, 28]. In many studies, the role of hormonal contraceptives is controversial [25, 29-31]. The mechanism of action of COC is by suppression of ovulation; COC inhibits pituitary production and secretion of Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH), and blunts the mid-cycle surge of both hormones, which inhibits follicular development, ovulation, and corpus lutein formation. This process also blocks normal hypothalamic production of gonadotropin-releasing hormone. Cyclofem also prevents pregnancy by thickening the cervical mucus. The ovaries and adrenal glands produce about 50% of the circulating testosterone, whereas the other 50% comes from peripheral conversion of precursor steroids from the ovaries and adrenals. Most circulating testosterone is bound to Sex Hormone-Binding Globulin (SHBG) and albumin, which leaves only 1% to 2%, as active free testosterone [32]. Estrogen-containing hormonal contraceptives increase levels of sex-hormone-binding globulin, leading to a reduction in free testosterone levels; this effect is greater in formulations with higher estrogen content [33]. Strufaldi et al. (2010) argued the theory that low androgen levels in COC users contribute to a low libido, which was investigated by 2 studies. Females, who had taken androgen and higher free testosterone levels, showed significantly improved sexual function [33-35]. However, Shifren et al. (2000) found that androgen therapy is efficient in the treatment of females, who had Hypoactive Sexual Desire Disorder (HSDD) [36]. It is unknown whether this effect is linked to the conversion of androgens into estrogen or only to the direct effect of androgen. The authors did not measure testosterone in their study. The females, who are more sensitive to testosterone changes, showed more sexual problems [37]. The role of sex hormones in protecting female's sexual health is not clearly known. Hormonal effects may be influenced by many factors, including, biological such as adrenal hormone deficiency, effects of environmental enzymes in cells, sensitivity of estrogen receptors, effects of the aromatase enzyme, number of sex steroid receptors, and proteins [38]. Sexual problems related to hormonal contraception methods may be due to different physiological responses to hormone levels, so that the rate of sexual problems in some communities is less than in other communities [39]. However, the role of testosterone in female's sexual arousal should be taken into consideration. The females, who are more sensitive to testosterone changes, experience more sexual problems [40]. In this study, cyclofem estrogen level is several times as ethinyl estradiol. Once the estradiol cypionate enters circulation, it is hydrolyzed into estradiol, an endogenously occurring estrogen and inactive cyclopentane propionic acid. Estradiol cypionate is also an esterified form of natural 17 β -estradiol. The natural estrogens are metabolized faster than synthetic ethinyl estradiol and have a lower bio-availability [41, 42]. The binding of the estrogen to the body's receptors occurs as estradiol rather than ethinyl estradiol [43].

Simber et al. (2007) concluded that a significant reduction in concentration of endometrial vessels occurs with cyclofem compared to before use and normal endometrium [44]. Estrogen levels have a complex effect on sexual function [45]. Changes in volume of vaginal wall and clitoris and local blood flow can also effect response to sexual stimuli [46]. Absence of estrogen cannot prevent vaginal lubrication, required for sexual stimuli [45]. Hormonal balance is essential in sexual function. Estradiol and nitric oxide play an important role in vaginal epithelium, and they also help vaginal lubrication. This is evident in cases of reduced estrogen level [46]. The role for estrogens is considerably more controversial [47]. The significant effect of estrogen on sexual interest and arousal is not supported by evidence [48]. In one study, the authors found a significant difference in sexual desire and arousal between COC and cyclofem users. The main reason for sexual activity was to preserve human generation. Sexual activity was initiated with sexual desire, which is generated by emotional and physical causes [49]. The sexual side effects of hormonal contraceptives are not well studied, particularly with regards to the impact on libido [32]. Many studies have investigated the relationship between estrogen dose and sexual desire [30, 33, 50]. Pastor et al. (2013) observed that different doses of COCs have different effects. For COCs containing 20 to 35 μ g EE, there was no change in sexual desire in most females [51]. Sexual arousal is highly complicated and can not be clearly differentiated from desire [35]. Sexual desire may be influenced by biological, psychological, and cultural factors [25]. Biological factors do not act independently from environmental factors [52].

Sexual functioning is a complex process that depends on the neurological, vascular, and endocrine systems, and psychosocial factors, such as self-concept and self-esteem [5]. Female's sexual interest is influenced by their mental state, beliefs and values, expectations and sexual orientation, priorities and environmental conditions. Sexuality, desire, and arousal are severely affected by mental health and feelings of the sexual partner during the sexual intercourse [53]. Mental health is a predictor of sexual function. Females, who have good mental health have less distress about sex compared to other females. In fact, females with sexual problems received lower scores in the assessment of their mental health [54]. Self-confidence plays an important role in sexual issues. It is essential for establishing a balance, adaptation, and individual successes. Self-confidence is a pleasant internal energy for mental relations, which can cause neuropsychological balance and mental health of the person. If this balance is not achieved, the person is exposed to stress [53]. Females with problems in sexual desire and arousal show anxiety, low self-confidence, and lack of emotional stability [54]. Love and emotional attachments can boost sexual desire [40]. Previous pleasurable experiences and favorable feelings toward their spouse can effect sexual satisfaction in females, which can prevent sexual dysfunction in cases of reduced sexual hormones [4]. Despite numerous studies, the role of sex hormones on sexual function was doubtful and their predictions is not possible for all females, who use hormonal contraceptives. The authors recommend further studies in this area.

Study Limitations and Strengths

The current study had a number of limitations. Spouses'

sexual dysfunction was not assessed. An effective factor in sexual function is spouse's age and his health status. With aging of the spouse, erectile and ejaculatory dysfunction increases, and daily fatigue, work, and stress can effect sexual function of males, and naturally that of females. Against this strength, the descriptive comparative design limited our causative assessment of sexual dysfunction in 2 types hormonal contraceptives. This study was conducted in Tehran province, so may not reflect the general population of Iran. In conclusion, although females have to use contraceptives to prevent unwanted pregnancies, they should choose the right contraceptive with the least effect on their sex life. Thus, we emphasize sexual counseling as part of family planning counseling. When counseling a females on contraceptive options, it is important to present potential positive and negative implications.

ETHICAL CONSIDERATION

issues, informed consent, conflict of interest, plagiarism, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc. have been considered carefully by the authors.

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CONFLICTS OF INTEREST

The authors declared that they had no competing interests. Also, the views expressed in this paper were those of the authors.

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AUTHORS' CONTRIBUTION

All authors participated in the study design, literature review, data collection, analysis, and editing of the manuscript.

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