*Eastern Journal of Medicine 20 (2015) 24-29*

Original Article

# Effects of different progestins in oral contraceptives on sexual function and well-being of women

Orkun Çetin[a,*], Seda Keskin[b], Fatma Ferda Verit[c], Oğuz Yücel[c]

[a]*Department of Gynecology and Obstetrics, Yüzüncü Yıl University, Medical Faculty, Van, Turkey*
[b]*Department of Gynecology and Obstetrics, Ordu University Training and Research Hospital, Ordu, Turkey*
[c]*Department of Gynecology and Obstetrics, Süleymaniye Maternity Training and Research Hospital, İstanbul, Turkey*

**Abstract.** To compare the effects of different progestins in combined oral contraceptives (COC) on sexual functions and well-being of women. In this prospective and observational study, 52 participants used drosperinone, 48 participants used gestodene, 55 participants used levonorgestrele and 60 participants used non- hormonal contraception. All participants completed the Female Sexual Function Index (FSFI) and Beck Depression Inventory (BDI) at baseline and after six cycles of treatment.

There was a statistically significant improvement between FSFI scores at baseline and after six cycles of treatment compared with each other. There was no significant difference between FSFI scores compared with each other.

In the hormonal contraception group, there was a statistically significant increase between BDI scores at baseline and after six cycles of treatment. In each hormonal contraception subgroup, there was no significant difference between BDI scores. These data show that COC pills make positive effects on female sexuality. Androgenic or antiandrogenic progestins have similar improvements on female sexual function. In addition, COC pills have negative impacts on depression.

Key words: Oral contraceptives, progestins, sexual function, well-being

## 1. Introduction

Over time, many formulations of combined oral contraceptives (COC) have been developed, and today's pill contains lower doses of synthetic estrogen; almost all COCs that are currently being used contain ethynil estradiol (EE) as the estrogen component. The primary way in which COCs differ among each other is in the progestin component. Progestins have been refined and improved upon since the pill was introduced. Newer pills containing progestins such as desogestrel, norgestimate, and drosperinone are less androgenic, which under certain circumstances is desirable, such as for the treatment of acne or hirsutism. For example, drosperinone is the only progestin FDA approved in the United States that blocks the androgen receptor and is truly antiandrogenic, even without the addition of EE (1). However, as will be discussed further, medications that interfere with androgen levels will likely have a negative impact on female sexual function.

Female sexual function is influenced by a multitude of factors including sexual hormones (estrogens, androgens and progestins), which elicit different effects on vaginal tissue and the central nervous system (2).

The estrogen component, which is metabolized in the liver, leads to increased hepatic production of sex hormone binding globulin (SHBG). Although some progestins decrease SHBG, the over all effect of all COCs is an elevation in SHBG levels. Increased SHBG levels leads to decreased levels of free testosterone. Thus, all COCs are antiandrogenic, although some formulations, depending on the specific progestin, are more so than others (3). Testesterone has a high affinity for SHBG, and high SHBG serum levels can therefore reduce free testosterone levels, which are important for sexual function (4).

Given that COCs are a highly effective form of contraception, they may help to eliminate the fear of pregnancy, presumably provide a more relaxed and enjoyable sexual experience (5). An association between COCs and sexual

*Corresponding Author: Dr. Orkun Çetin
Adress: Department of Gynecology and Obstetrics, Yüzüncü Yıl University, Medical Faculty, 65300 Van,Turkey
Phone: 0 532 591 0205
E- mail: drorkuncetin34@hotmail.com
Received: 22.03.2014
Accepted: 30.04.2014

dysfunction has already been suggested (6), although the extent of the effects remain unclear (7,8).

The aim of this prospective and observational investigation was to study and compare the effects of COCs containing different progestins (levonorgestrel, gestodene, drosperinone) on the sexual function and well- being of women.

*1. 1. Measurements*

We used the well-established female sexual function index (FSFI) by Rosen et al (9) to analyze female sexual function (10). The questionnaire was validated in the Turkish language. In brief, a total score (Questions 1-19) is obtained in addition to six subscores: desire (Q 1-2), arousal (Q 3-6), lubrication (Q 7-10),orgasm (Q 11-13), satisfaction (Q 14-16) and pain (Q 17-19). Total FSFI score below 30 means impaired sexual function. In addition to the FSFI questions, we also asked 11 questions concerning the parcipitants' means of contraception and changes in contraception and recent sexual activity. Beck Depression Inventory (BDI) is a 21 questions multipl choice self report inventory that is one of the most widely used instruments for measuring the severity of depression (11). Scores 10-16 showing mild depression, scores 17-29 indicate moderate depression while scores above 30 indicating severe depression.

*1. 2. Study design*

This prospective and observational study was conducted in Süleymaniye Training and Research Hospital, a single center in İstanbul, Türkiye between February 2012 to March 2013. The study protocol was approved by the local independent ethics committees, and all participants provided written informed consent before study enrollment. The study was conducted in accordance with the amended version of the Declaration of Helsinki and in compliance with the principles of Good Clinical Practice.

Participants were divided into four groups using computer generated randomization table. Randomization was conducted according to a block randomization scheme prepared by the responsible statistician.

*1. 3. Patients*

Healthy women aged 18-35 years requesting contraception were eligible to participate in this study. The exclusion criteria included: pregnancy or lactation; contraindications to contraceptive use; body mass index > 30 kg/ m²; uncontrolled thyroid disorders; clinically signicifant findings that may worsen with hormonal treatment; depression or a history of depression in the last year; vascular disease or factors that predispose to vascular disease; diabetes mellitus or impaired glucose tolerance; sickle cell anemia; disturbance of lipid metabolism; use of medication that are known to affect the metabolism or pharmacokinetics of COCs such as hydantoins, barbiturates, rifampicin or St. John's wart; uncontrolled hypertension and; malignant or premalignant tumors. Women were excluded from the study if they had a sexual aversion/ phobic disorder, sexual pain disorder/ dispareunia. All participants' baseline total score of FSFI was above 30.

Of the 262 participants in the study, 215 took part in the follow- up. 15 (5.7%) of them were relocated outside the study region, 12 (4.6%) of them had demanded deletion of their address and the contact failed for 20 (7.6%) participants. The final continue rate of the study was 82.1% (215/ 262).

*1. 4. Treatment*

The patients were examined at a baseline screening unit to confirm their eligibility, medical history and general health status.

Patients requesting oral contraception received six cycles of 30 mcg EE- 3 mg drosperinone, 30 mcg EE- 75 mcg gestodene and 30 mcg EE- 150 mcg LNG administered according to the conventional 21/7 regimen. Treatment in cyle 1 began on the first day of menstrual bleeding, which was considered as day of 1 of the treatment cycle.

52 of them received 30 mcg EE- 3 mg drosperinone, 48 of them received 30 mcg EE- 75 mcg gestodene, 55 of them received 30 mcg EE- 150 mcg LNG and 60 of them who rejected any hormonal method or intrauterine contraceptive device but using traditional methods and condom for contraception were enrolled for non-hormonal contraception group. All the clinical assessments were performed at baseline before treatment and after six cycles of treatment with hormonal contraception. All participants completed the FSFI and BDI at baseline and after treatment. No pregnancy was observed in the study group.

*1. 5. Statistical analysis*

All data were analyzed using the statistical package for the social sciences version 16.5. Paired samples student's t-test, ANOVA, Pearson Chi- square tests were used for evaluating the differences before and after treatment.

## 2. Results

A total of 215 women aged 18-35 years were enrolled in the study and completed the request questionnaires.

Table 1. Characteristics of patients

| Group | Drosperinone | LNG | Gestodene | Non- hormonal Contraception |
|---|---|---|---|---|
| Age | 27.92 | 26.79 | 25.44 | 26.37 |
| Pregnancy | 2.37 | 2.48 | 2.02 | 2.22 |
| BMI (kg/m²) | 24.8 | 24.5 | 24.93 | 24.88 |

LNG: Levonorgestrele, BMI: Body Mass Index.

Table 2. Socio- demoghraphic datas of patients

| Group | Drosperinone (%) | LNG (%) | Gestodene (%) | Non- hormonal Contraception (%) |
|---|---|---|---|---|
| Housewife | 73.1 | 79.2 | 74.5 | 81.7 |
| Worker | 26.9 | 20.8 | 25.5 | 18.3 |
| Primary school graduate | 67.3 | 70.8 | 72.7 | 66.7 |
| High school graduate | 17.3 | 16.7 | 12.7 | 16.7 |
| College graduate | 5.8 | 4.2 | 5.5 | 5 |
| Illiterate | 9.6 | 8.3 | 9.1 | 11.7 |

LNG: Levonorgestrele.

Table 3. The total FSFI scores of patients at baseline and after six cycles of treatment

| Group | Drosperinone | LNG | Gestodene | Non- hormonal Contraception | p (inter group comparison) |
|---|---|---|---|---|---|
| Baseline FSFI score | 30.70 | 30.75 | 30.74 | 30.61 | 0.378 |
| FSFI score after treatment | 34.03 | 34.11 | 34.13 | 30.86 | 0.000 |
| p (intra group comparison) | 0.000 | 0.000 | 0.000 | 0.440 | |

FSFI: Female Sexual Function Index, LNG: Levonorgestrele.
$p < 0.05$ is statistically significant.

Table 4. The total BDI scores of patients at baseline and after six cycles of treatment

| Group | Drosperinone | LNG | Gestodene | Non- hormonal Contraception | p (intergroup comparison) |
|---|---|---|---|---|---|
| Baseline BDI score | 8.27 | 7.8 | 8.18 | 8.08 | 0.263 |
| BDI score after treatment | 11.98 | 11.83 | 11.95 | 9.18 | 0.004 |
| p (intra group comparison) | 0.000 | 0.000 | 0.000 | 0.353 | |

BDI: Beck Depression Inventory, LNG: Levonorgestrele.
$p < 0.05$ is statistically significant.

Age distribution revealled that women were between 18 and 35 years old, and between participants 155 were using hormonal contraception and 60 were not. Among the women using hormonal contraception, 52 used 30 mcg EE- 3 mg drosperinone, 48 used 30 mcg EE- 75 mcg gestodene, 55 used 30 mcg EE- 150 mcg LNG. Table 1 lists the COCs used and baseline characteristics of patients. There were no significant differences in patient characteristics at baseline between four groups.

Table 2 lists sociodemographic data of patients. There were no significant differences in patients' sociodemographic data between four groups.

Table 3 shows the total FSFI scores at baseline and after treatment for six cycles with hormonal and non-hormonal contraception. The median baseline total score of FSFI for the groups was 30.69. There was no significant difference between four groups (p=0.378). The median total score of FSFI after treatment for six cycles was 33.18.

Table 4 shows the total BDI scores at baseline and after six cycles of treatment with hormonal and non-hormonal contraception. The median total baseline score of BDI for the groups was 8.08. There was no significant differences between four groups (p=0.263). The median total score of BDI after treatment of six cycles was 11.15.

Table 3 shows the scores of FSFI for drosperinone, gestodene and LNG groups; there were a statistically significant improvement between the scores at baseline and after six cycles

of treatment (p=0.000). There were no differences in FSFI scores between three groups (drosperinone, gestodene, LNG) (p=0.905). In non-hormonal contraception group; there were no differences between the scores of FSFI at baseline and after six cycles of treatment (p=0.440) Hormonal contraception users (drosperinone, gestodene, LNG) had higher FSFI scores than non-hormonal contraception users after six cycles of treatment. There was a statistically difference between two groups (p=0.000).

Table 4 shows the scores of BDI for drosperinone, gestodene and LNG groups; there were a significant increase between the scores at baseline and after six cycles of treatment (p: 0,000). This change of BDI score was significant for clinical depression. There were no differences in BDI scores between three groups (drosperinone, gestodene, LNG) (p=0.844). In non-hormonal contraception goup; there was not a significant change between the BDI scores at baseline and after six cycles of treatment (p=0.353). Hormonal contraception users had higher BDI scores than non- hormonal contraception users after six cycles of treatment. (p=0.004).

## 3. Discussion

The oral contraceptive pill is a highly effective and reversible form of contraception. Unlike the male condom, the women have control over this method of contraception. Although there are many formulations of COC, in clinical trials, when used perfectly, the failure rate is less than 1%. Additionally they have a well-established safety profile with serious adverse events such as myocardial infarction and thromboembolic events occurring rarely (12). It appears, however, that some third generation COC become a higher risk of thromboembolism than second generation COC. Lastly, there are many non- contraceptive health benefits associated with the pill, including a decreased overall risk of some gynecologic cancers as well as decreased mortality (13-15).

As noted earlier, since COCs were introduced half a century ago, there have been relatively few studies on their impact on female sexuality. Most of these studies were not controlled trials and the results are conflicting, suggesting that there are many ways in which COC could positively or negatively effect female sexual function. Alternatively, there are so many factors affect female sexual function that these factors may display any effect (positive or negative) attributable to COC.

Ovarian dysfunction and hormonal unbalance of endogenous or iatrogenic origin are associated with reduced sexual desire and disturbance of sexual arousal (16). Testosterone may play a key role in mediating hormonal effects on sexual function, as many factors that induce changes in free testosterone serum levels (17,18). Compounds that bind to the androgen receptor and trigger androgenic effects may also be involved. Progestins used in COCs possess partial androgenic or antiandrogenic properties (4), and these progestins can modulate synthesis of SHBG, an important regulator of free testosterone serum levels. It is well known that EE can influence the synthesis of various liver proteins, including SHBG, and that SHBG synthesis may be dependent on the EE dose (4). These hormonal functions led to the hypothesis that the sex hormones in COCs might influence female sexual function via their modes of action and that these influences may be dose dependent.

Graham et al (19) investigated the serum levels of total testosterone, free testosterone and dehydroepiandrosteron sulfate during COC intake using the same progestin. Significant decreases were found in three months. Their findings also suggested a statistical correlation between low total testosterone and free testosterone levels and the frequency of sexual thoughts. However some women showed no loss of sexual interest despite low testosterone levels. The authors concluded that some women might be more sensitive to changes in testosterone levels. Panzer et al (3), investigated SHBG serum levels in 124 women with sexual dysfunction who were users and nonusers of COCs. The SHBG levels were up to four times higher in users, and total FSFI scores were also lower. Warnock et al (20), measured SHBG, total testosterone and free testosterone serum levels in 106 women with sexual dysfunction, 43 of whom were COC users. Among COC users, SHBG levels were higher and total and free testosterone levels lower than in nonusers, but both had sexual dysfunctions.

Mc Coy and Matyas in their questionnare based study, hypothesized that because COCs are known to decrease free testosterone, the COC users would experience fever thoughts and fantasies than nonusers. Contrary to their prediction, COC users reported higher frequency of sexual thoughts, fantasies and interest than nonusers (21).

In our study, based on the validated and well-established FSFI, we found significant difference between COC and non hormonal contraception users at baseline and after the six cycles of

treatment. COC users had higher FSFI scores than non hormonal contraception method users after the six cycles of treatment. Caruso et al, prospectively assessed the effects of 30 mcg EE- 3 mg drosperinone on sexual behavior in 80 women age 19- 31 compared with baseline, women reported increased sexual enjoyment, orgasm frequency and satisfaction with sexual activity (22). A recent study comparing 30 mcg EE- 3 mg drosperinone with another pill with 30 mcg EE- 150 mcg LNG found that in both groups, the majority of women experienced no change in libido (23). Two very recent trials by Caruso et al assessing the effects of specific COC on quality of sexual life demonstrated a positive effect on libido (24). In our study we compared 30 mcg EE- 3 mg drosperinone, 30 mcg EE- 75 mcg gestodene and 30 mcg EE- 150 mcg LNG by FSFI scores at baseline and after six cycles of treatment. We found no significant differences between three groups. But, at all of the three groups' total FSFI scores had a significant increase after six cycles of treatment, as demonstrated in Caruso et al' s studies above.

Mood- related side effects, such as irritability, mood swings and depressive symptoms, are among the major reasons for discontinuing COCs in women (25). On the other hand, a majority of the women report unchanged or improved mood while on COCs (26). In the prospective studies, increased anxiety and increased depressive mood were reported in 7 and 10% of women on COCs, respectively (27). Whereas discontinuation rates owing to adverse mood symptoms were as high as 14- 21% (28). A history of depression, a high level of psychological distress prior to COC use and socioeconomic factors increase the risk of becoming depressed when taking COCs (25). In our study; we found significant difference between COC and non-hormonal contraception users in BDI scores at baseline and after six cycles of treatment. COC users had higher BDI scores than non-hormonal contraception users after six cycles of treatment, which was consistent with the studies mentioned above. In hormonal contraception subgroup; there was no significant difference between three groups (drosperinone, gestoden, LNG) in BDI scores after six cycles of treatment. In each hormonal contraception group; there was a significant increase in BDI scores after six cycles of treatment comparing with baseline. This change of the BDI score was significant for clinical depression.

One should note as a limitation of our study, its relatively small sample size and lack of data related to possible confounding factors such as diet and physical activity, since these parameters are important in restoration of ovarian function and improvement in body composition (29,30). Nevertheless, our prospective observational study design enable us to evaluate potential impacts of different androgenic and antiandrogenic COCs and non-hormonal contraception on sexual functions and depression. Another limitation is that we did not collect laboratory measurements to support our clinical findings. (FSFI scores) Because both hormone and SHBG levels can vary widely and can be influenced by many factors. And the last limitation is that we report depression rates based on scores in screening tests that are outside the normal range and confirmation of depression by clinical assessment was not included in our study design.

When counseling a woman on contraceptive options, it is important to present potential positive and negative implications. Studies have shown that women who discontinue COC often choose a less effective method or no method of contraception, increasing their risk of pregnancy and COCs are known to have many health benefits (31). While side effects such as breast tenderness and weight gain are well documented, sexual side effects are not well studied. Particularly with regard to impact on libido. This is likely due to the fact that female libido is complex, and it is therefore difficult to reliably predict how its may be affected by COC. Based on current literature, the majority of which pertains to COC, it seems there are mixed effects on libido.

In conclusion; according to our investigation, treatment with COCs for six cycles have found positive effects on female sexuality. There was no difference between androgenic or antiandrogenic progestins in COCs on female sexual functions. In addition; we found that COCs could have negative effects on symptoms of depression.

## References


1. Fuhrmann U, Frattenmacher R, Slater EP, Fritzemeier KH. The novel progestin drospirenone and its natural counter part progesterone: Biochemical profile and antiandrogenic potential. Contraception 1996; 54: 243-251.
2. Goldstein I, Traish A, Munarriz R. The role of sex steroid hormones in female sexual function and dysfunction. Clin Obstet Gynecol 2004; 47: 471-484.
3. Panzer C, Wise S, Fantini G, et al. Impact of oral contraceptives on sex hormone binding globulin and androgen levels: A retrospective study in women with sexual dysfunction. J Sex Med 2006; 3: 104-113.

4. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. Climacteric 2005; 8(Suppl 1): 3-63.
5. Gold R. Rekindling efforts to prevent unplanned pregnancy: A matter of “equity and common sense”. Guttmacher Policy Rev 2006; 9: 2-6.
6. Bitzer J. Contraception and sexuality. Ther Umsch 1994; 51: 110-114.
7. Davis AR, Castano PM. Oral contraceptives and libido in women. Annu Rev Sex Res 2004; 15: 297-320.
8. Witting K, Santtila P, Jern P, et al. Evaluation of the Female Sexual Function Index in a population based sample from Finland. Arch Sex Behav 2008; 37: 912-924.
9. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000; 26: 191-208.
10. Daker-White G. Reliable and valid self-report outcome measures in sexual (dys)function: a systematic review. Arch Sex Behav 2002; 31: 197-209.
11. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-571.
12. Blanco-Molina A, Monreal M. Venousthromboembolism in women taking hormonal contraceptives. Expert Rev Cardiovasc Ther 2010; 8: 211-215.
13. Cibula D, Gompel A, Mueck AO, et al. Hormonal contraception and risk of cancer. Hum Reprod Update 2010; 16: 631-650.
14. Hannaford PC, Selvaraj S, Elliott AM, et al. Cancer risk amongusers of oral contraceptives: Cohort data from the Royal College of General Practitioner’s Oral ContraceptionStudy. BMJ 2007; 335: 651.
15. Hannaford PC, Iversen L, Macfarlane TV, et al. Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. BMJ 2010; 340: 927.
16. Goldstein IMC, Meston CR, Davis SR, et al. Women's sexual function and dysfunction: study, diagnosis and treatment. New York: Taylor & Francis; 2006.
17. Bhasin S, Enzlin P, Coviello A, Basson R. Sexual dysfunction in men and women with endocrine disorders. Lancet 2007; 369: 597-611.
18. Kurdoglu Z, Usul SY, Tasdemir M, Kurdoglu M. Evaluation of the relationship between endogenous gonadotropins and female sexual function and psychological status in predialysis and hemodialysis patients Gynecol Endocrinol 2012; 28: 336-339.
19. Graham CA, Bancroft J, Doll HA, Greco T, Tanner A. Does oral contraceptive-induced reduction in free testosterone adversely affect the sexuality ormood of women? Psychoneuroendocrinology 2007; 32: 246-255.
20. Warnock JK, Clayton A, Croft J, Segraves R, Boggs FC. Comparison of androgens in women with hypoactive sexual desire disorder: those on combined oral contraceptives (COCs) vs. those not on COCs. J Sex Med 2006; 3: 878-882.
21. McCoy NL, Matyas JR. Oral contraceptivesandsexuality in universitywomen. Arch Sex Behav 1996; 25: 73-90.
22. Caruso S, Agnello C, Intelisano G, et al. Prospective study on sexual behavior of women using 30 microg ethinyl estradiol and 3 mg drospirenone oral contraceptive. Contraception 2005; 72: 19-23.
23. Kelly S, Davies E, Fearns S, et al. Effects of oral contraceptives containing ethinyl estradiol with either drospirenone or levonorgestrel on various parameters associated with well-being in healthywomen: A randomized, single-blind, parallel-group, multi centre study. Clin Drug Investig 2010; 30: 325-336.
24. Caruso S, Agnello C, Romano M, et al. 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.
25. Oinonen KA, Mazmanian D. To what extent do oral contraceptives influence mood and affect? J Affect Disord 2002; 70: 229-240.
26. Joffe H, Cohen LS, Harlow BL. Impact of oral contraceptive pill use on premenstrual mood: predictors of improvement and deterioration. Am J Obstet Gynecol 2003; 189: 1523-1530.
27. Ernst U, Baumgartner L, Bauer U, Janssen G. Improvement of quality of life in women using a low-dose desogestrel- containing contraceptive: results of an observational clinical evaluation. Eur J Contracept Reprod Health Care 2002; 7: 238-243.
28. Larsson G, Blohm F, Sundell G, Andersch B, Milsom I. A longitudinal study of birth control and pregnancy outcome among women in a Swedish population. Contraception 1997; 56: 9-16.
29. Palomba S, Falbo A, Giallauria F, et al. Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in over weight and obese patients with polycystic ovary syndrome: a randomized controlled trial. Hum Reprod 2010; 25: 2783-2791.
30. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Life style changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev 2011; 7: CD007506.
31. Grady WR, Billy JO, Klepinger DH. Contraceptive method switching in the United States. Perspect Sex Reprod Health 2002; 34: 135-145.