THE EUROPEAN JOURNAL OF CONTRACEPTION & REPRODUCTIVE HEALTH CARE
2024, VOL. 29, NO. 3, 103–108
https://doi.org/10.1080/13625187.2024.2332302

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Correlation of sexual desire with sexual hormone binding globulin and free androgen index in women using combined contraceptives

Salvatore Caruso[a], Giuseppe Caruso[b], Marco Iraci Sareri[b], Federica Di Guardo[b], Giosuè Giordano Incognito[b] and Marco Palumbo[b]

[a]Research Center for the PreDiCT Study -Department of Biomedical and Biotechnological Sciences, School of Medicine, University of Catania, Catania, Italy; [b]Department of General Surgery and Medical Surgical Specialties, Gynecological Clinic, School of Medicine, University of Catania, Catania, Italy

ABSTRACT

Purpose: To correlate the sexual desire levels with sexual hormone binding globulin and free androgen index in women taking different types of hormonal contraceptives (HCs) containing ethinylestradiol (EE), oestradiol valerate (E2V), 17β-oestradiol (E2), or estetrol (E4), combined or in phasic formulation with different progestogens having antiandrogenic properties.

Methods: Three hundred and sixty-seven women (age range 18-46) participated in the study. SHBG and total testosterone (TT) were measured, and the Free Androgen Index (FAI) was calculated. The Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS) questionnaires were used to assess sexual function and distress, respectively.

Results: The highest SHBG values and the lowest FAIs were obtained of women on HCs containing EE than those of women on HCs containing E2V/17β E2 or E4 ($p < 0.001$). Desire scores and FSFI total scores were lower in women on HCs with EE than in those using HCs containing E2V, 17β E2, or E4 ($p \leq 0.001$). The women who were on HCs containing EE reported FSDS levels higher than those containing all the other types of oestrogen. Finally, sexual desire and FSFI total scores had a negative correlation with the SHBG values and a positive correlation with FAI percentage ($p \leq 0.0001$).

Conclusions: A minority of women using HCs with EE might experience a decreased sexual desire. This was not observed in women on HCs containing E2V, 17 E2, or E4. To avoid HC discontinuation, due to sexual desire reduction, HCs having minor antiandrogenic effects could be taken into consideration.

ARTICLE HISTORY
Received 31 January 2024
Revised 13 March 2024
Accepted 13 March 2024

KEYWORDS
Hormonal contraceptives; estetrol; oestradiol; ethinylestradiol; free androgen index; sexual desire; sexual hormone binding globulin

Introduction

Today, contraceptive counselling aims to improve the acceptability of a hormonal or non-hormonal contraceptive, not only as a method chosen to avoid pregnancy but also as having neutral or positive effects on the sexual function of women [1]. However, an open debate remains on the effects of combined hormonal contraceptives (CHCs) on sexual desire [2,3].

Androgens may have an important biological role in sexual desire and arousal in women [4], although androgen sensitivity and sexual function differ among women [5,6]. CHCs could negatively modify the sexual activity of women by increasing the androgen-binding protein and producing hypoandrogenism, mainly in androgen-sensitive women [7–9], resulting in hypoactive sexual desire [10].

Specifically, sex hormone-binding globulin (SHBG) is a carrier protein synthesised in hepatocytes; its synthesis has been shown to be highly sensitive to oestrogens and androgens [11]. Oestrogens increase SHBG levels in a quality and dose-dependent manner in women on CHCs, whereas progestogens may contribute to modify these levels to a varying extent depending on their quantity and quality [12]. The effect of a CHC formulation on SHBG thus appears to reflect the balance between oestrogenic and androgenic activities [13].

CHCs are the most frequently used among short-acting reversible contraceptives (SARC) [14]. Since the beginning of hormonal contraception, EE has been the only oestrogen used in CHCs. The main advances achieved in CHCs have been the reduction of EE dosages and the production of more selective progestogens having antiandrogenic activity, which improved the tolerability of CHCs [15]. The use of oestrogens that show a greater resemblance to endogenous hormones, the natural oestrogens, has been the most recent advancement in combined and phasic formulation HC development. New pills containing oestradiol valerate (E2V) or 17β-oestradiol (E2) have been introduced for more than a decade in oral contraception. They have fewer adverse effects than EE [16]. E2V is associated with dienogest (DNG) with a 26/2 four-phasic regimen [17], and E2 is combined with nomegestrol acetate (NomAc) with a 24/4 regimen [18]. Both progestogens have antiandrogenic activity and high progestogen potency effects. The use of natural oestrogens in combination with progestogens further improves tolerability and minimises the effects of EE on

CONTACT Salvatore Caruso scaruso@unict.it Research Center for the PreDiCT Study -Department of Biomedical and Biotechnological Sciences, School of Medicine University of Catania, Via Etnea 251 - 95124 Catania, Italy

hepatic metabolism and hepatic protein synthesis, and has more favourable lipid and haemostatic profiles [19,20].

Recently, Estetrol (E4) has been introduced in modern oral contraception. E4 is produced by the foetal liver during pregnancy and reaches the maternal circulation. E4 is the first native oestrogen with selective tissue activity (NEST); in fact, it exhibits activation of nuclear ERα and inhibition of membrane ERβ, which leads to tissue-specific actions including the breast. E4 15 mg is combined with drospirenone (DRSP) 3 mg, with a 24-days of active pill use followed by a 4-day hormone-free interval regimen [21,22]. A modest increase in SHBG levels, equal to 44.5%, was observed in women on E4/DRSP, considerably less than the 306.3% observed in women who used CHC containing EE [23].

The main aim of the current study was to correlate sexual desire with SHBG levels and free androgen index (FAI) in women on CHCs containing different qualitative and quantitative oestrogens.

Material and methods

This study was performed at the Family Planning Centre of the Obstetrics and Gynecological Pathology, Department of General Surgery and Medical Surgical Specialties, School of Medicine, University of Catania, Italy. The study protocol was conformed to the ethical guidelines of the 2013 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 enrolment was from January 2018 to January 2023.

At enrolment, 458 women -aged 18 to 46 years- gave their consent to participate in the study. All women were on HCs, according to WHO medical eligibility criteria [24]. Women without sexual activity and/or having or have had sexual dysfunction, and/or living with a partner with sexual dysfunction and/or having conflictual relationships were excluded from the study.

Instruments

Each woman underwent a sexual history interview. To define female sexual dysfunction (FSD), more recent definitions, nomenclature, and classifications were used [25].

Sexual behaviour was assessed using the self-administered Female Sexual Function Index (FSFI) validated in the Italian gynecological population [26]. The FSFI consists of six domains, which include desire (two items), arousal (four items), lubrication (four items), orgasm (three items), satisfaction (three items), and pain (three items), answered on a five-point Likert scale, ranging from 0 (no sexual activity) or 1 (never/very low) to 5 (always/very high). A score is calculated for each of the six domains and the total score is obtained by summing all the items. The total score range is 2–36. A cut-off of ≤26.55 is usually accepted for diagnosis of sexual dysfunction in premenopausal women. In addition, to confirm sexual dysfunction, it must cause significant personal distress to the woman. Therefore, the 12-item Female Sexual Distress Scale (FSDS) questionnaire was used, with a maximum score of 48. An FSDS score ≥15 corresponds to clinically significant distress [27]. In summary, women with an FSFI score of ≤26.55 are considered to have sexual dysfunction if they have an FSDS score ≥15.

Finally, a peripheral blood sample was taken from each woman after enrolment to measure total testosterone (TT, ng/dL) and SHBG (nmol/L) by ELISA (Elecsys© Systems 2010, Roche). The Free Androgen Index (FAI) was calculated by using FAI = [TT/SHBG (nmol/L)]100.

Statistical analysis

Analysis of variance was used to compare the data between groups, and the Bonferroni test was adopted for multiple comparisons. To compare the intergroup FSFI scores, the Mann-Whitney U-test was used. Correlation analyses with Pearson's r coefficient were performed to examine the relationships between sexual desire scores and FSFI scores with SHBG values and FAI. Scores are presented as the mean ± SD. The result was statistically significant when $p < 0.05$. Statistical analysis was carried out using the Primer of Biostatistics statistical computer package (Glantz SA, New York, USA: McGraw-Hill, Inc. 1997).

Results

After enrolment, 91 (19.9%) women did not complete the study. Of them, 22 (24.2%) had not responded to all items of the FSFI questionnaire, and 69 (75.8%) withdrew their consent before undergoing the blood test. Consequently, 367 women (aged 18 to 46 years) constituted the sample undergoing clinical and statistical evaluation. Each woman declared having the same sexual partner, and a good quality of relationship for the last three months. No woman referred to have had adverse events in their last three months of CHC usage. Moreover, 20.6% of women on E2V/DNG, 28.3% on 17β-E2/NomAc, 8.9% on EE20/DRSP, and 12.2% on E4/DRSP referred to be in amenorrhoea. This did not cause any of them to discontinue their contraceptive.

Table 1 shows the number and percentage of women distributed according to the type, regimen, route of administration, and duration of usage in months of each HC.

Table 1. Number and percentage of women distributed according to the type, regimen, route of administration, and duration of usage in months of each hormone contraceptive.

Subjects *N* = 367 (%)	Regimen/formulation	Oestrogen	Progestogen	Route of administration	Duration of usageMonths (mean ± SD)
45 (12.2)	24/4 -combined	EE 20μg	DRSP 3 mg	Oral	33 ± 8
52 (14.2)	21/7- combined	EE 30μg	DRSP 3 mg	Oral	32 ± 9
39 (10.7)	21/7- combined	EE 30μg	DNG 2 mg	Oral	29 ± 6
52 (14.2)	21/7 - combined	EE 15μg	ENG 120 μg	Vaginal ring	26 ± 9
63(17.2)	26/2 -quadriphasic	E2V	DNG	Oral	36 ± 10
67 (18.2)	24/4 -combined	17β-E2 1.5mg	NomAc 2.5mg	Oral	38 ± 9
49 (13.4)	24/4 - combined	E4 14.2 mg	DRSP 3 mg	Oral	10 ± 5

EE: Ethinylestradiol; E2V: Oestradiol Valerate; E2: Oestradiol; E4: Estetrol; DRSP: Drospirenone; DNG: Dienogest; ENG: Etonogestrel; NomAC: Nomegestrolo Acetate.

Table 2. Total testosterone (TT), sexual hormone binding globulin (SHBG), and free androgen index (FAI) percentages in women during hormonal contraceptive intake.

Types of hormonal contraceptive	TT (nmol/L)	SHBG (nmol/L)	FAI (%)
EE 20 µg/DRSP 3 mg	1.5 ± 0.9	154 ± 18	0.9 ± 0.04
EE 30 µg/DRSP 3 mg	1.4 ± 0.2	180 ± 22	0.7 ± 0.03
EE 30 µg/DNG 2 mg	1.6 ± 0.1	178 ± 21	0.9 ± 0.05
EE 15 µg/ENG 120 µg	1.7 ± 0.1	159 ± 19	1.1 ± 0.05
E2V/DNG	1.6 ± 0.2	57 ± 7	2.8 ± 0.15
17β E2 1.5 mg/NomAc 2.5 mg	1.7 ± 0.1	61 ± 9	2.7 ± 0.14
E4 14.2 mg/DRSP 3 mg	1.6 ± 0.4	45 ± 6	3.1 ± 0.17

EE: Ethinylestradiol; E2V: Oestradiol Valerate; E2: Oestradiol; E4: Estetrol; DRSP: Drospirenone; DNG: Dienogest; ENG: Etonogestrel; NomAC: Nomegestrolo Acetate. Values are expressed as means ± SD.

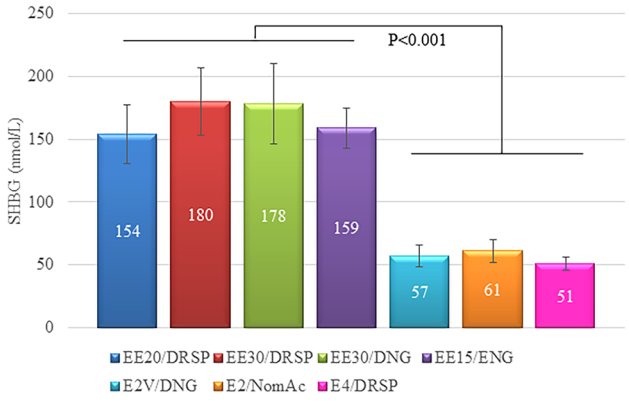

Figure 1. Effects of seven hormonal contraceptives (20 µg EE/3 mg DRSP, 30 µg EE/3 mg DRSP, 30 µg EE/2 mg DNG, 15 µg EE/120 µg ENG, E2V/DNG, 1.5 mg 17β-E2/2.5 mg NomAc, 14.2 mg E4/3 mg DRSP) on serum concentration of sexual hormone binding globulin (SHBG). The number inside each column refers the average of SHBG.

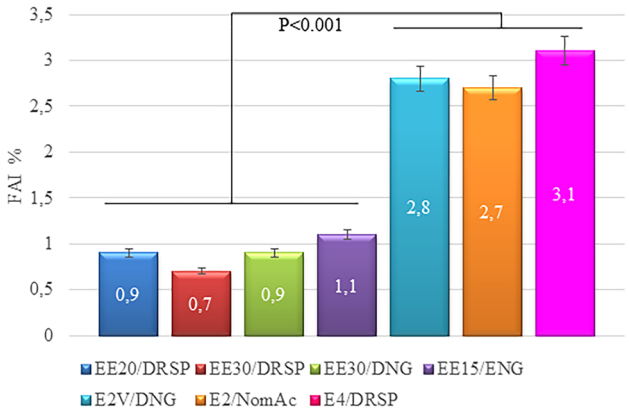

Figure 2. Effects of seven hormonal contraceptives (20 µg EE/3 mg DRSP, 30 µg EE/3 mg DRSP, 30 µg EE/2 mg DNG, 15 µg EE/120 µg ENG, E2V/DNG, 1.5 mg 17β-E2/2.5 mg NomAc, 14.2 mg E4/3 mg DRSP) on free androgen index (FAI) percentages. The number inside each column refers the average of FAI.

Seven subgroups were obtained. Specifically, 188 (51.2%) women were using HCs containing EE, 130 (35.4%) containing E2V or 17β E2, and 49 (13.4%) containing E4. Moreover, all progestogens had no androgenic activity. Table 2 shows TT (nmol/L) and SHBG (nmol/L) values by which was possible to calculate the FAI percentages.

Figure 1 shows the SHBG values obtained from each subgroup of women on HCs. Particularly, all values of SHBG of women on CHCs containing EE were statistically significantly higher than those of women on HCs containing E2V, 17β-E2, or E4 ($p < 0.001$). Consequently, the lowest FAI percentages were achieved by women using CHCs containing EE, while the highest ones were by women using HCs with E2V, 17β-E2 and E4 ($p < 0.001$), (Figure 2).

Table 3 shows the sexual feelings and responses to the FSFI questionnaire of the seven subgroups. Desire scores were lower in women on CHCs with EE than in those using HCs containing E2V, 17β-E2, or E4 ($p \leq 0.001$). Moreover, no statistically significant differences in desire scores there were among subgroups of women on CHCs with EE ($p \leq 0.7$), neither among women on HCs with E2V, 17β-E2 or E4 ($p \leq 0.8$); but the desire scores were higher in women on HCs with E2V,17β-E2 and E4 compared to those with EE ($p < 0.001$). However, it should be noted that the women who were using vaginal rings, containing EE 15 µg, had better sexual desire than those on oral HCs containing a higher quantity of EE ($p \leq 0.01$), but still a worse sexual desire than those on HCs containing E2V or 17β-E2, or E4. A similar trend was observed for arousal, lubrication, orgasm, satisfaction, and dyspareunia. Consequently, the FSFI total scores of women on HCs with E2V or 17β-E2, or E4 were all above the cut-off (>26.55), while those of women on CHCs containing EE were below the cut-off (<26.55), ($p < 0.001$). Only women on vaginal rings had FSFI scores above the cut-off, although lower than those using HCs with E2V or 17β-E2, or E4 ($p \leq 0.001$). Interestingly, women who were on CHCs containing EE reported personal sexual distress scores slightly higher than the cut-off (>15). These values were 16.1 ± 1.8, 17.3 ± 1.9, and 17.6 ± 1.7 for women on EE 20 µg/DRSP 3 mg, EE 30 µg/DRSP 3 mg, and EE 30 µg/DNG 2 mg, respectively. After handing in the FSFI questionnaire with her answers, each woman, if she deemed it necessary, was invited to ask for counselling on her current contraceptive and sexual function. Of all samples, 11 (24.5%) women on EE 20 µg/DRSP 3 mg, 18 (34.6%) on EE 30 µg/DRSP 3 mg, 13 (33.3%) on EE 30 µg/DNG 2 mg, and 6 (11.5%) using vaginal ring requested a consultation exclusively for the negative impact of CHC on sexual desire. However, switching to another contraceptive was not among the objectives of the current study, therefore no data were reported.

Interestingly, sexual desire scores had a negative correlation with the SHBG values (r= −0.95; $p < 0.001$) and a positive correlation with FAI percentage ($r = 0.97$; $p < 0.0001$). Similarly, FSFI total scores had a negative correlation with SHBG values (r= −0.90; $p < 0.004$), and a positive correlation with FAI percentage ($r = 0.90$; $p < 0.005$). Conversely, FSDS scores had a positive correlation with SHBG value ($r = 0.78$; $p < 0.03$), and a negative correlation with FAI percentage (r= −0.77; $p < 0.04$).

Finally, a correlation was still observed in women using CHCs with EE; it was negative between FSFI and SHBG (r= −0.52; $p = 0.04$) and positive between FSFI and FAI ($r = 0.70$; $p = 0.03$). Interestingly, a positive correlation was observed between FSDS and SHBG ($r = 0.60$) and a negative

Table 3. Female sexual function index (FSFI) and Female sexual distress scale (FSDS) scores in women during seven hormonal contraceptives intake.

FSFI items	EE 20μg DRSP 3 mg n. 45	EE 30μg DRSP 3 mg n. 52	EE 30μg DNG 2 mg n. 39	EE 15μg ENG 120 μg n. 52	E2V DNG n. 63	17β-E2 1.5mg Nomac 2.5 mg n. 67	E4 14.2 mg DRSP 3 mg n. 49
Desire	3.1 ± 1.2	3.4 ± 1.7	3.3 ± 1.5	4 ± 1.1	5.1 ± 1.7	5.2 ± 1.3	5.4 ± 1.4
Arousal	3.5 ± 1.3	3.5 ± 1.4	3.4 ± 1.3	4.1 ± 1.5	4.5 ± 1.1	4.6 ± 1.1	4.8 ± 1.3
Lubrication	4.2 ± 1.7	3.5 ± 1.5	3.6 ± 1.7	4.9 ± 1.4	4.9 ± 1.5	5.2 ± 1.2	5.3 ± 12
Orgasm	4.1 ± 1.3	2.9 ± 1.6	3.1 ± 2.2	4.4 ± 1.3	4.7 ± 1.4	4.8 ± 1.1	5.1 ± 1.5
Satisfaction	3.3 ± 1.2	3.2 ± 1.4	3.1 ± 1.3	4.8 ± 1.2	4.9 ± 1.3	4.9 ± 1.2	5.4 ± 1.4
Dyspareunia	4.4 ± 1.5	3.3 ± 1.7	3.2 ± 1.7	5 ± 1.5	5.3 ± 1.8	5.5 ± 1.2	5.5 ± 1.7
FSFI score	22.6 ± 1.8	19.8 ± 2.7	19.7 ± 2.3	27.2 ± 1.5	29.4 ± 1.9	30.2 ± 1.6	31.5 ± 1.5
FSDS score	16.1 ± 1.5	17.1 ± 1.3	17.6 ± 1.2	11.5 ± 1.6	1 0.1 ± 1.5	9.3 ± 1.4	10.4 ± 1.1

Notes. EE: Ethinylestradiol; E2V: Oestradiol Valerate; E2: Oestradiol; E4: Estetrol; DRSP: Drospirenone; DNG: Dienogest; ENG: Etonogestrel; NomAC: Nomegestrolo Acetate.
Values are expressed as means ± SD.

correlation between FSDS and FAI (r= −0.50), but both were not statistically significant ($p > 0.05$). Regarding women on CHCs with E2 and E4, a negative correlation between FSFI and SHBG (r= −0.60: $p = 0.01$) and a positive correlation between FSFI and FAI ($r = 0.53$; $p = 0.02$) were observed. Furthermore, there was a negative correlation between FSDS and SHBG (r= −0.60: $p = 0.01$) and a positive correlation between FSFI and FAI ($r = 0.53$; $p = 0.02$)

Discussion

Findings and interpretation

This study measured the sexual desire levels in women on CHCs. Firstly, women who were using CHCs containing EE had higher levels of SHBG and a lower percentage of FAI than women who were on CHCs containing natural oestrogens (E2V or 17β-E2), or native oestrogen (E4). Moreover, sexual desire and FSFI scores positively correlated with FAI, and negatively with SHBG, and vice versa, FSDS negatively correlated with FAI and positively with SHBG. This trend was also noticed by analysing the aforementioned correlations of two subgroups consisting, on the one hand, of women who were using CHCs with EE and, on the other hand, of those who were using CHCs with E2 and E4, except for the correlation between FSDS and SHBG or FAI in the women on CHC with EE, which was not statistically significant. Therefore, even if sexual function appears to be statistically significantly correlated with SHBG (negatively) and FAI (positively) in women using CHCs with EE, and the FSDS scores are dysfunctional, sexual distress does not seem to be a decisively influential aspect in all women. These data reflect what happens in clinical practice: in fact, not all women who use CHCs with a strong androgenic component suffer from hypoactive sexual desire or sexual dysfunction. Moreover, FSFI scores were below the cut-off (≤26.55) in women on CHC with EE, and above it in those on CHC with E2V, 17β-E2, and E4. This may also have been due to all the other sexual function items included in the FSFI questionnaire such as arousal, lubrication, orgasm, satisfaction, and dyspareunia, which reached lower values in women on CHCs with EE compared to those with E2V, 17β-E2, and E4.

Beyond the common adverse events, such as weight gain, abnormal menstrual bleeding, breast pain, and migraine, that may cause discontinuation of CHCs [28], a decrease in sexual desire could be experienced by the users as a result of circulating androgen decrease [29]. However, the effects of CHCs on sexual function remain controversial. A minority of CHC users undergo changes in sexual function, such as sexual desire disorder [30,31]. This was also highlighted in the current study, in which a minority of women who were using CHCs with EE stated that they experienced a decreased sexual desire.

Physiologically, ovarian steroids appear to modulate the sexual activity of women. A linear correlation between sexual activity and hormonal profile was previously observed, specifically for TT and FAI, the highest values of which were observed during the periovulatory phase. In women who were not using hormonal contraceptives or who were taking non-hormonal contraceptives, sexual desire increased during the periovulatory phase of the menstrual cycle [32]. At midcycle, the gradual increase in oestrogen promotes the thinning of the cervical mucus, which results in watery secretion with low viscoelasticity. Moreover, androgens are required for the synthesis of the glycoproteins needed for mucous formation [33]; this may explain the decreased vaginal lubrication noted by some women when they are using a hormonal contraceptive with antiandrogenic activity. In addition, hypoandrogenism may cause the onset of vulvodynia and contribute to impaired vaginal lubrication, particularly in women with polymorphisms of the androgen receptor gene [34].

Differences and similarities in relation to other studies

Most of the studies highlighting the negative effect of CHCs on sexual function did not consider the type, regimen, and route of administration, but CHCs as a whole. Recently, authors observed that antiandrogenic properties of CHCs, containing EE and antiandrogenic progestins, provoke decreases in vaginal blood flow and lubrication, and female sexual arousal disorder [35].

A literature review and meta-analysis demonstrated that CHCs containing EE decrease circulating levels of TT and free T and increase SBHG concentrations. Due to the SHBG increase, free T levels decreased twice as much as TT [13]. The EE dose and progestin type of the CHC did not influence the reduction of TT and free T directly, but both affected SHBG [36].

Strengths and weaknesses

The strength of the study consists in having investigated bio-hormonal areas that could influence adherence to hormonal contraception. The negative effects on sexual desire that some women experience when using hormonal contraceptives with high antiandrogenic activity may cause

discontinuation of the method. Four EE-containing CHCs were studied for the aims of the study, as they differ from each other in the amount of EE and the quality of the progestogen, and in their regimen and route of administration. Moreover, they are CHCs commonly prescribed by doctors to women requiring contraception. Today, being able to choose between hormonal contraceptives with a lower antiandrogenic impact can improve the quality of a woman's sexual life. Therefore, if there is no need to use hormonal contraceptives for non-contraceptive purposes, for example, to modulate hyperandrogenic events, choosing a contraceptive containing natural oestrogens or native oestrogen may be best. The main limit of our study was the small sample number in each subgroup of CHC users, but also to have enrolled women who were on CHCs containing only antiandrogenic progestins and were using SARC. Moreover, no women on transdermal contraceptives participated in the study. To measure the SHBG and FAI values in women on CHCs containing progestin with androgenic properties, or only-progestin contraceptives, and correlate them with the sexual desire of users, future studies will be needed.

Clinical implications and future research

Women may independently decide to discontinue hormonal contraception not only for method-related reasons, such as weight gain, abnormal menstrual bleeding, breast pain, and migraine but also for not commonly known reasons, such as sexual disorders. Unlike the former, desire disorders that could arise during the intake of HCs are unlikely to be reported to the physicians, mainly due to the woman's embarrassment in talking about it. The risk of HC discontinuation is to have an unwanted pregnancy. Currently, CHCs containing EE and progestin with antiandrogenic properties could be used for non-contraceptive purposes, for example, to treat hyperandrogenic disorders. The reduction of aesthetic signs due to hyperandrogenism usually improves the quality of life and sexual health of users, based on CHC compounds and regimens [37]. Contrarily, when CHCs are prescribed for better risk-free sexuality, such as to avoid pregnancy, the effects of their high antiandrogenic activity could affect the quality of sexual life in some women. This could be the reason to use CHCs with lower antiandrogenic impact, mainly used CHCs containing natural or native oestrogens. However, not all women with reduced androgenicity experience sexual disorders or complain that they have suffered from sexual changes since they started using COC. Different biopsychosocial variables can contribute to modifying the quality of the sexual life of a woman. On the other hand, one person, unlike another, may experience a reduction in androgens, and this gives further meaning to the difference between individuals, but also the concept of tailoring contraception.

Conclusion

Today some strategies for better HC usage could be taken into consideration to improve a woman's sexual health, such as switching from dysfunctional to more functional methods [38]. Therefore, it would be important to investigate the sexual activity of a woman to whom HC is about to be prescribed to better choose which one would be most suitable for her. We have learned not to expect one hormonal contraceptive to be the solution to all problems [9]. The concept that all women are different and variably sensitive to HC steroids has to be emphasised [39]. We have entered an era where it is possible to adopt the concept of tailoring an HC to a particular woman, thanks to the fact of being able to choose HCs no longer only with EE, but also among those containing natural oestrogens or native oestrogen, even if they are combined with antiandrogenic progestin. This choice could allow the antiandrogenic effects of HCs to be reduced.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

ORCID

Salvatore Caruso http://orcid.org/0000-0002-1387-0932
Giuseppe Caruso http://orcid.org/0000-0001-9854-4441
Marco Iraci Sareri http://orcid.org/0000-0003-2433-4841
Federica Di Guardo http://orcid.org/0000-0002-2562-7323
Giosuè Giordano Incognito http://orcid.org/0000-0002-1818-0105
Marco Palumbo http://orcid.org/0000-0002-0467-4892

References

[1] Caruso S, Malandrino C, Cicero C, et al. Quality of sexual life of women on oral contraceptive continued-regimen: pilot study. J Sex Med. 2013;10(2):460–466. doi: 10.1111/j.1743-6109.2012.03004.x.
[2] Malmborg A, Brynte L, Falk G, et al. Sexual function changes attributed to hormonal contraception use - a qualitative study of women experiencing negative effects. Eur J Contracept Reprod Health Care. 2020;25(3):169–175. doi: 10.1080/13625187.2020.1736545.
[3] Caruso S, Palermo G, Caruso G, et al. How does contraceptive use affect women's sexuality? A novel look at sexual acceptability. J Clin Med. 2022;11(3):810. doi: 10.3390/jcm11030810.
[4] Whitton K, Baber R. Androgen-based therapies in women. Best Pract Res Clin Endocrinol Metab. 2023; May38(1):101783. doi: 10.1016/j.beem.2023.101783.
[5] Bancroft J, Graham CA. The varied nature of women's sexuality: unresolved issues and a theoretical approach. Horm Behav. 2011;59(5):717–729. doi: 10.1016/j.yhbeh.2011.01.005.
[6] Wåhlin-Jacobsen S, Kristensen E, Pedersen AT, et al. Androgens and psychosocial factors related to sexual dysfunctions in premenopausal women*: *2016 ISSM female sexual dysfunction prize. J Sex Med. 2017;14(3):366–379. doi: 10.1016/j.jsxm.2016.12.237.
[7] Greco T, Graham CA, Bancroft J, et al. The effects of oral contraceptives on androgen levels and their relevance to premenstrual mood and sexual interest: a comparison of two triphasic formulations containing norgestimate and either 35 or 25 microg of ethinyl estradiol. Contraception. 2007;76(1):8–17. doi: 10.1016/j.contraception.2007.04.002.
[8] Davis SR, Bitzer J, Giraldi A, et al. 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(12):3069–3079. doi: 10.1111/jsm.12310.
[9] Caruso S, Cianci S, Cariola M, et al. Improvement of low sexual desire due to antiandrogenic combined oral contraceptives after switching to an oral contraceptive containing 17β-Estradiol. J Womens Health (Larchmt). 2017;26(7):728–734. doi: 10.1089/jwh.2016.5801.
[10] Schaffir J. Hormonal contraception and sexual desire: a critical review. J Sex Marital Ther. 2006;32(4):305–314. doi: 10.1080/00926230600666311.

[11] Mansour D, Verhoeven C, Sommer W, et al. Efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17β-oestradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen. Eur J Contracept Reprod Health Care. 2011;16(6):430–443. doi: 10.3109/13625187.2011.614029.

[12] Odlind V, Milsom I, Persson I, et al. Can changes in sex hormone binding globulin predict the risk of venous thromboembolism with combined oral contraceptive pills? Acta Obstet Gynecol Scand. 2002;81(6):482–490.

[13] Zimmerman Y, Eijkemans MJ, Coelingh Bennink HJ, et al. The effect of combined oral contraception on testosterone levels in healthy women: a systematic review and meta-analysis. Hum Reprod Update. 2014;20(1):76–105. doi: 10.1093/humupd/dmt038.

[14] United Nations Department of Economic and Social Affairs Population Division. World contraceptive use. 2007. http://www.un.org/esa/population/publications/contraceptive2013/contraceptive_2013_table.pdf

[15] Rosenberg MJ, Meyers A, Roy V. Effi cacy, cycle control, and side effects of low- and lower-dose oral contraceptives: a randomized trial of 20 micrograms and 35 micrograms estrogen preparations. Contraception. 1999;60(6):321–32 9. doi: 10.1016/s0010-7824(99)00109-2.

[16] Hoffmann H, Moore C, Zimmermann H, et al. Approaches to the replacement of ethinylestradiol by natural 17beta-estradiol in combined oral contraceptives. Exp Toxicol Pathol. 1998;50(4-6):458–464. doi: 10.1016/s0940-2993(98)80034-1.

[17] Hoy SM, Scott LJ. Estradiol valerate/dienogest in oral contraception. Drugs. 2009;69(12):1635–1646. doi: 10.2165/11202820-000000000-00000.

[18] Christin-Maitre S, Serfaty D, Chabbert-Buffet N, et al. Comparison of a 24-day and a 21-day pill regimen for the novel combined oral contraceptive, nomegestrol acetate and 17beta-estradiol (NOMAC/E2): a double-blind, randomized study. Hum Reprod. 2011;26(6):1338–1347. doi: 10.1093/humrep/der058.

[19] Sitruk-Ware R, Nath A. Metabolic effects of contraceptive steroids. Rev Endocr Metab Disord. 2011;12(2):63–75. doi: 10.1007/s11154-011-9182-4.

[20] Ågren UM, Anttila M, Mäenpää-Liukko K, et al. Effects of a monophasic combined oral contraceptive containing nomegestrol acetate and 17β-oestradiol compared with one containing levonorgestrel and ethinylestradiol on haemostasis, lipids and carbohydrate metabolism. Eur J Contracept Reprod Health Care. 201116;16(6):444–457. doi: 10.3109/13625187.2011.604450.

[21] Douxfils J, Morimont L, Gaspard U, et al. Estetrol is not a SERM but a NEST and has a specific safety profile on coagulation. Thromb Res. 2022; Sep232:148–150. S0049-3848(22)00387-5 doi: 10.1016/j.thromres.2022.09.007.

[22] Gemzell-Danielsson K, Cagnacci A, Chabbert-Buffet N, et al. A novel estetrol-containing combined oral contraceptive: european expert panel review. Eur J Contracept Reprod Health Care. 2022;27(5):373–383. doi: 10.1080/13625187.2022.2093850.

[23] Mawet M, Maillard C, Klipping C, et al. Unique effects on hepatic function, lipid metabolism, bone and growth endocrine parameters of estetrol in combined oral contraceptives. Eur J Contracept Reprod Health Care. 2015;20(6):463–475. doi: 10.3109/13625187.2015.1068934.

[24] World Health Organization. Medical eligibility criteria for contraceptive use. 5th edition. Geneva: world Health Organization; 2015

[25] Parish SJ, Cottler-Casanova S, Clayton AH, et al. The evolution of the female sexual disorder/dysfunction definitions, nomenclature, and classifications: a review of DSM, ICSM, ISSWSH, and ICD. Sex Med Rev. 2021;9(1):36–56. doi: 10.1016/j.sxmr.2020.05.001.

[26] Nappi RE, Albani F, Vaccaro P, et al. Use of the italian translation of the female sexual function index (FSFI) in routine gynecological practice. Gynecol Endocrinol. 2008;24(4):214–219. doi: 10.1080/09513590801925596.

[27] Derogatis LR, Rosen R, Leiblum S, et al. The female sexual distress scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. J Sex Marital Ther. 2002;28(4):317–330. doi: 10.1080/00926230290001448.

[28] Fruzzetti F, Perini D, Fornaciari L, et al. Discontinuation of modern hormonal contraceptives: an italian survey. Eur J Contracept Reprod Health Care. 2016;21(6):449–454. doi: 10.1080/13625187.2016.1234598.

[29] Casado-Espada NM, de Alarcón R, de la Iglesia-Larrad JI, et al. Hormonal contraceptives, female sexual dysfunction, and managing strategies: a review. JCM. 2019;8(6):908. doi: 10.3390/jcm8060908.

[30] Both S, Lew-Starowicz M, Luria M, et al. Hormonal contraception and female sexuality: position statements from the European Society of Sexual Medicine (ESSM). J Sex Med. 2019;16(11):1681–1695. doi: 10.1016/j.jsxm.2019.08.005.

[31] Buggio L, Barbara G, Facchin F, Ghezzi L, Dridi D, Vercellini P. The influence of hormonal contraception on depression and female sexuality: a narrative review of the literature. Gynecol Endocrinol. 2022;38:193–201. doi: 10.1080/09513590.2021.2016693.

[32] Caruso S, Agnello C, Malandrino C, et al. Do hormones influence women's sex? Sexual activity over the menstrual cycle. J Sex Med. 2014;11(1):211–221. doi: 10.1111/jsm.12348.

[33] Kennedy TG, Armstrong DT. Induction of vaginal mucification in rats with testosterone and 17β-hydroxy-5α-androstan-3-one. Steroids. 1976;27(3):423–430. doi: 10.1016/0039-128x(76)90061-1.

[34] Goldstein AT, Belkin ZR, Krapf JM, et al. Poly-morphisms of the androgen receptor gene and hormonal contraceptive induced provoked vestibulodynia. J Sex Med. 2014;11(11):2764–2771. doi: 10.1111/jsm.12668.

[35] Handy AB, McMahon LN, Goldstein I, et al. Reduction in genital sexual arousal varies by type of oral contraceptive pill. J Sex Med. 2023;20(8):1094–1102. doi: 10.1093/jsxmed/qdad072.

[36] Morgante G, Cappelli V, Troìa L, et al. Evaluation of different antiandrogenic progestins on clinical and biochemical variables in polycystic ovary syndrome. Eur J Contracept Reprod Health Care. 2020;25(3):176–181. doi: 10.1080/13625187.2020.1736546.

[37] Caruso S, Rugolo S, Agnello C, et al. Quality of sexual life in hyperandrogenic women treated with an oral contraceptive containing chlormadinone acetate. J Sex Med. 2009;6(12):3376–3384. doi: 10.1111/j.1743-6109.2009.01529.x.

[38] Wellings K, Brima N, Sadler K, et al. Stopping and switching contraceptive methods: findings from contessa, a prospective longitudinal study of women of reproductive age in England. Contraception. 2015;91(1):57–66. doi: 10.1016/j.contraception.2014.09.008.

[39] De Leo V, Musacchio MC, Cappelli V, et al. Hormonal contraceptives: pharmacology tailored to women's health. Hum Reprod Update. 2016;22(5):634–646. doi: 10.1093/humupd/dmw016.