The European Journal of Contraception and Reproductive Health Care, 2013; 18: 27–43

The influence of combined oral contraceptives on female sexual desire: A systematic review

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ABSTRACT **Objectives** To determine the relationship between the use of combined oral contraceptives (COCs) and sexual desire based on a systematic review of the literature.

Methods MEDLINE Complete, Google Scholar and the Cochrane Library were searched for articles published between 1975 and 2011, reporting the effects of oral contraceptives on sexual desire. Reports fully meeting all the predefined criteria were analysed and included in a final reference list. In addition, a review of the reference list of selected articles was carried out.

Results We evaluated 36 studies (1978–2011; 13,673 women). Of the COC users ($n = 8,422$), 85% reported an increase ($n = 1,826$) or no change ($n = 5,358$) in libido and 15% reported a decrease ($n = 1,238$). We found no significant difference in sexual desire in the case of COCs with 20–35 μg ethinylestradiol; libido decreased only with pills containing 15 μg ethinylestradiol.

Conclusions The majority of COC users report no significant change in libido although in most studies a decline in plasma levels of free testosterone and an increase in those of sex hormone binding globulin were observed.

KEYWORDS Combined oral contraceptives; Sexual desire; Libido; Androgen; Testosterone; Oestrogen; Female sexuality

INTRODUCTION

Combined oral contraceptives (COCs) contain an oestrogen (until recently: ethinylestradiol [EE]) and a progestin of varying potency and androgenicity. A short time ago COCs containing oestradiol (E_2) or oestradiol valerate (E_2V) became available as well. Use of COCs is associated with certain somatic (e.g., venous and pulmonary thromboembolism) or psychogenic complications (e.g., dysphoria, depression, hypoactive sexual desire disorder [HSDD]) that may necessitate discontinuation. This is why the search for new types of COCs with minimal side effects is continuing[1,2].

Sexual desire is the perception of the need for sexual gratification. It is also termed 'libido', 'motivation', or 'interest', and these terms are often used interchangeably in the literature. Sexual desire is a highly distinctive individual observation, and it is a complex of physical, cognitive, emotional, and interpersonal characteristics[3].

In line with the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text-Revised* (DSM-IV-TR),

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DOI: 10.3109/13625187.2012.728643

HSDD is characterised by persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity[4]. The American Urological Association Foundation defines sexual interest/desire disorder as absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies, and a lack of responsive desire[5].

The oestrogen component in COCs causes an increase in the production of the sex hormone binding globulin (SHBG), which causes circulating free testosterone levels to drop. COCs depress the production of androgens in the ovaries and adrenal glands[6]. They also inhibit the enzyme 5-alpha reductase, which converts testosterone into dihydrotestosterone, the latter being the form that binds to cellular receptors[7–9]. These facts support the hypothesis that COCs, by lowering androgen levels, could decrease sexual desire in users[10]. Some authors consider the pill to be a modulator of sexual desire[11,12]. The changes in androgen levels vary depending on the individual user concerned[6]. Although the levels of total and free testosterone are reduced in COC users, sexual interest is not always affected[13]. Even though an androgen deficit is considered to be a cause of HSDD in women, the precise role of testosterone in female sexuality has yet to be elucidated[14–18].

Many investigators have studied the relationship between the use of COCs and a decline in sexual desire[10,11,13,19–24]. In contrast, other studies have demonstrated a mostly neutral or positive influence of COCs on libido[1,12,25–35].

By comparing representative studies, we aimed to determine the effect of COCs on sexual desire in relation to the changes in free testosterone levels and also to certain non-hormonal aspects.

METHODS

We conducted a MEDLINE Complete, Google Scholar and Cochrane Library search for papers in the English language published from 1975 to 2011 in which the effects of COCs on sexual desire were reported. The search terms relevant to contraception were used as follows: *oral contraceptives* OR *contraception* AND *female sexuality*, *oral contraceptives* OR *contraception* AND *sexual desire* OR *libido*, *oral contraceptives* AND *androgens* AND *sexual desire*, *oral contraceptives* AND *testosterone* AND *sexual desire*. Further, five textbooks[4,6,7,9,15] were found suitable and included in the reference list. The reference list of review articles was searched in order to identify papers, which were not found by an Internet search. In the course of the selection process, first we examined the titles and abstracts retrieved from the electronic search. We combined the search results into one file and removed duplicates manually. Of the large quantity of retrieved papers, only a few had evaluated the effects of the pill on female sexual desire. Unsuitable articles were excluded based on the following criteria: studies referring solely to contraception other than COCs (e.g., contraceptive rings, patches), studies wherein the age of respondents was lower than 18 years, and studies wherein COCs were examined in relation to other somatic or psychogenic illnesses. The full texts of the selected papers were retrieved and analysed again in order to be included in the reference list. Two articles were translated from the German and Portuguese languages, respectively. Additional screening was done based on the exclusion criterion that a study providing an insufficient conclusion related to the context of our review needed to be rejected. The process of selecting articles for this review is shown in Figure 1.

In addition, we reviewed the reference lists of the selected articles and included papers addressing other problems (e.g., female hyperandrogenism). A total of 67 papers (52 studies, ten reviews, and five book chapters) were compiled into a final reference list, the review articles and books chapter were retained as sources of potentially compelling references. Heterogeneity of data provided in the studies did not allow us to carry out a standard meta-analysis so we used a synthesis method. Synthesis involved data extraction and organisation into tables. When assessing the studies, we compared the studies based on their similar and contrasting findings. We used information for formulation and evaluation of our review as described by Rycroft-Malone *et al*. in their paper[36].

Of the 52 studies, 36 comparable studies were selected, which primarily addressed the effect of COCs on sexual desire. Of these 36 studies, 11 were prospective uncontrolled; eight, prospective controlled; six, randomised controlled; six, retrospective controlled; and five, retrospective uncontrolled.

In Table 1 we summarised for each of the 36 papers the following: the basic study characteristics, number of respondents in the study, number of COC users, age and origin of the respondents, study type, assessment technique, impact of COCs on free testosterone, libido and findings of the studies.

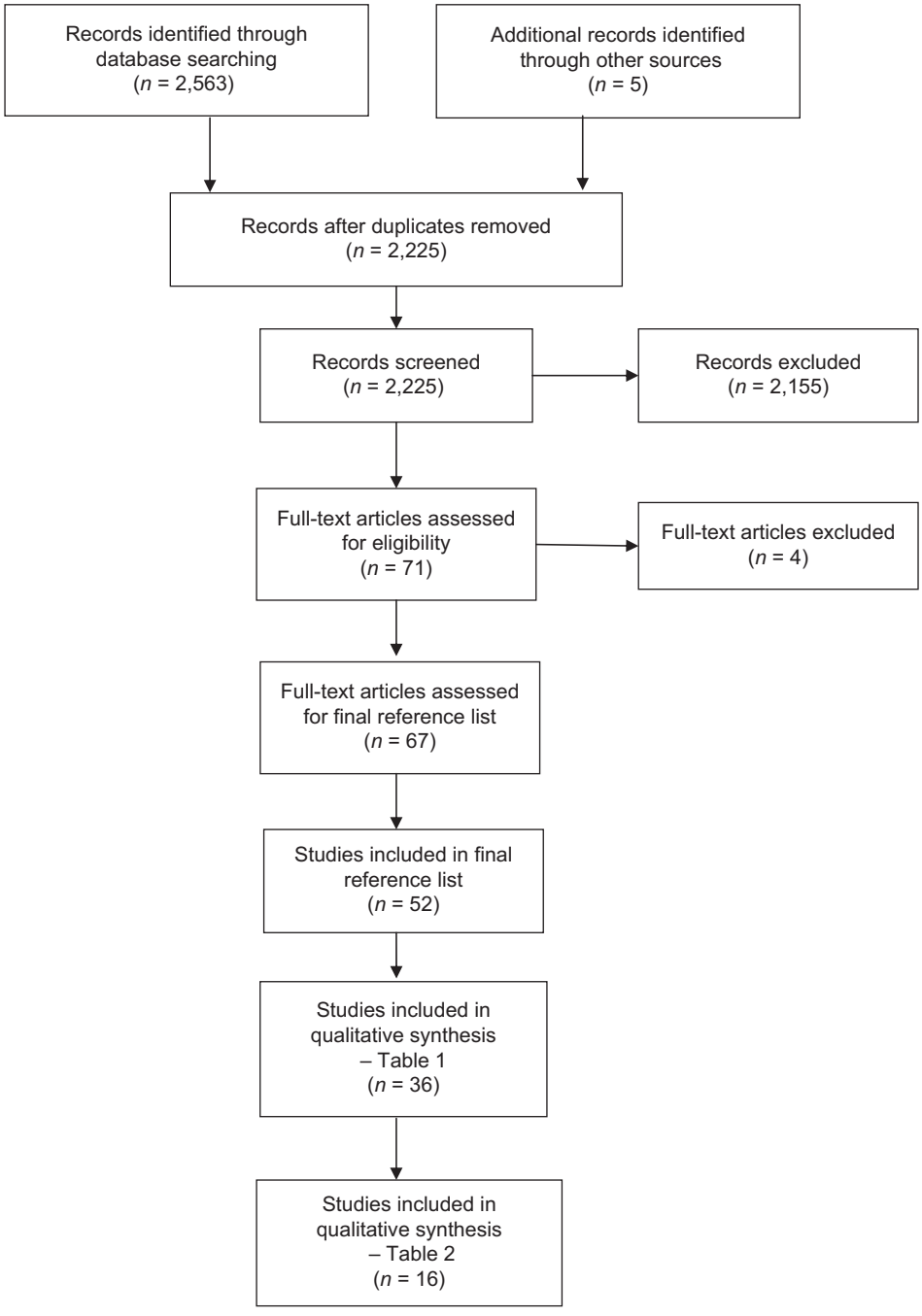

Figure 1 Selection process flow of papers.

To compare the effects of different EE doses and dosage regimen of COCs, Table 2 was constructed. For each of the 16 studies which were selected on the basis of the available data concerning EE doses and dosage regimen, the table again provides information on the number of COC users in the study, impact of COCs on free testosterone and SHBG levels, and impact on libido.

RESULTS

We analysed 36 heterogeneous studies published between 1978 and 2011 which were relevant to our topic and contained valid data. Most studies were controlled. Investigators examined the sexual desire of women of fertile age and residing in different regions

Table 1a Key characteristics of studies assessing impact of COC on sexual desire divided in four subgroups based on a number of respondents.

Author, year	*Country*	*COC users*	*Total number of respondents*	*Age (mean or range)*	*Type of study*	*Assessment technique*	*Impact of COCs on free testosterone levels*	*Impact of COCs on libido*	*Characteristics of study and (other) essential findings*
GROUP A									
Adams *et al.*, 1978[19]	USA	12	35	21–37	Prospective, controlled	Questionnaire	No change	No change	Female sexual activity unchanged while using COCs
Bancroft *et al.*, 1979[37]	UK	20	40	20	Prospective, controlled	Questionnaire, daily ratings, interviews	No change	No change	Administration of exogenous androstenedione failed to improve sexual function in COC users
Alexander *et al.*, 1990[25]	Canada	18	31	18+	Retrospective, controlled	Daily ratings	No change	Increase	COC users reported more satisfaction with their partners than nonusers
Graham and Sherwin, 1992[38]	Canada	20	45	29	Randomised, controlled	Daily ratings, VAS	No data	Decrease	COC users reported decrease of sexual interest in various phases of pill-driven cycle
Alexander and Sherwin, 1993[39]	Canada	19	19	18+	Retrospective uncontrolled	Daily ratings	Decrease	Increase	COC users were more satisfied with their sexual partners than nonusers
Sanders *et al.*, 2001[23]	USA	79	79	22	Prospective, uncontrolled	IRSF, SES	No data	Decrease	Certain women experienced adverse effects of COCs on sexuality
Guida *et al.*, 2004[31]	Italy	25	51	22–34	Prospective, controlled	IRSF, VAS	No data	Increase	General improvement of sexual functions in COC users

Caruso *et al.*, 2004[21]	Italy	48	48	18–35	Prospective, uncontrolled	PEQ	Decrease	Decrease	15 μg EE in COCs may cause vaginal dryness and worsen sexual functions
Caruso *et al.*, 2005[26]	Italy	80	80	19–31	Prospective, uncontrolled	PEQ	Decrease	No change	Improved vaginal lubrication, sexual arousal, and decreased dyspareunia were observed when using COCs with 30 μg EE but sexual desire unchanged
Oranratanaphan and Taneepanichskul, 2006[40]	Thailand	86	86	18–35	Prospective, randomised, controlled	FSFI	Decrease	Increase	Sexual desire in COC users is not decreased
Graham *et al.*, 2007[41]	USA	61	61	18–31	Retrospective, controlled	IRSF, SEQ	Decrease	No change	Some women may be more sensitive to changes in free testosterone than others, with effects on their mood and sexuality
Greco *et al.*, 2007[42]	USA	48	48	18–30	Retrospective, controlled	SDI, BDI, side effect questionnaire	Decrease	No change	No significant difference observed between COCs containing 25 μg and 35 μg EE
Caruso *et al.*, 2009[43]	Italy	72	72	18–32	Prospective, uncontrolled	SF-36, SPEQ	Decrease	Increase	The 30 μg EE and 2 mg CMA pill has an anti-androgenic effect and may improve sexual function

(*Continued*)

Table 1a (*Continued*)

Author, year	*Country*	*COC users*	*Total number of respondents*	*Age (mean or range)*	*Type of study*	*Assessment technique*	*Impact of COCs on free testosterone levels*	*Impact of COCs on libido*	*Characteristics of study and (other) essential findings*
Lee *et al.*, 2010[44]	USA	24	52	18–35	Prospective, controlled	FSFI, GSA, vulvalgesiometer	Decrease	Increase	COC with 20 μg EE reduces free testosterone but does not alter clitoral and vestibular sensation
Strufaldi *et al.*, 2010[45]	Brazil	97	97	28	Prospective, randomised controlled	FSFI	Decrease	Increase	Sexual desire score increased with COC containing 20 μg EE
Heiman *et al.*, 2011[46]	The Netherlands, USA	47	93	31	Prospective, controlled	SDM, BDI-II, AFSFO, FSFQ, SDI-2, DAS, SES, FSDS-R, vaginal photoplethysmograph	Decrease	No change	Women without HSDD showed lower levels of FT unlike women with HSDD
Caruso *et al.*, 2011[47]	Italy	57	57	18–48	Prospective, uncontrolled	SF-36, SPEQ	Decrease	Increase	Use of the E_2V/DNG multi-phasic pill seemed to have a positive effect on sexuality
Battaglia *et al.*, 2012[48]	Italy	22	22	18–35	Prospective, uncontrolled	2D US evaluation, colour Doppler, MFSQ	Decrease	Decrease	COC (30 μg EE and 3 mg DRSP) use is associated with a decrease in both libido and spontaneous arousability

GROUP B									
Fucs and Coutinho, 1975[49]	Portugal	73	113	18+	Prospective, uncontrolled	Interview, questionnaire	No data	Increase	COC may be useful for treatment of low libido
Gambrell *et al.*, 1976[50]	USA	211	211	20	Prospective, uncontrolled	Interview, questionnaire	No data	Increase	Improvement of sexual response after five years of COC use
Erkkola *et al.*, 1990[51]	Finland	162	162	20–40	Retrospective, multicentre uncontrolled	Interview	No data	Decrease	COC (35 μg EE and 2 mg CPA) use associated with reduced libido
Bancroft *et al.*, 1991[52]	Canada	55	108	18–28	Prospective, controlled	Questionnaire, Likert scale	Decrease	Increase	COC users had more frequent sexual intercourse
Graham *et al.*, 1995[13]	UK, the Philippines	50	150	32	Randomised, controlled	BDI, daily ratings, IRSF, SEQ	No data	Decrease	Changes in sexual interest are influenced by cultural factors
Sabatini and Cagiano, 2006[53]	Italy	186	280	30	Prospective, randomised controlled	Questionnaire, interview	No data	No change	COC use (20 μg EE) associated with small increase in sexual desire in 47% of cases
Panzer *et al.*, 2006[22]	USA	62	124	33	Retrospective, controlled	SDS, FSFI, BDI	Decrease	Decrease	Chronic SHBG elevation in COC users may be linked to sexual, metabolic, and mental health problems
Warnock *et al.*, 2006[10]	USA	43	106	22–50	Prospective, controlled	Laboratory assessment	Decrease	Decrease	COC users with HSDD have significantly lower androgen levels than nonusers with HSDD

(*Continued*)

Table 1a (*Continued*)

Author, year	*Country*	*COC users*	*Total number of respondents*	*Age (mean or range)*	*Type of study*	*Assessment technique*	*Impact of COCs on free testosterone levels*	*Impact of COCs on libido*	*Characteristics of study and (other) essential findings*
Skrzypulec and Drosdzol, 2008[54]	Poland	61	126	18+	Prospective, controlled	SF-36, FSFI	No data	Increase	Improvement of sexual function score among users of a COC containing 30 μg EE and 3 mg drospirenone
Caruso *et al.*, 2011[27]	Italy	115	115	18–37	Prospective, randomised controlled	SF-36, VAS, SPEQ	No data	Increase	24/4 COC cycle might have positive effect on the quality of sexual life
GROUP C									
McCoy and Matyas, 1996[12]	USA	153	364	18–26	Retrospective, controlled	MFSQ	No data	Increase	Women taking a triphasic COC experience greater sexual interest than those using a monophasic pill
Redmond *et al.*, 1999[33]	USA	228	462	18–49	Double blind, controlled	Interviews, monthly evaluations	No data	No change	The triphasic COC does not affect libido
Li *et al.*, 2004[32]	China	87	361	18–48	Prospective, uncontrolled	WHOQOL, DSFI	No data	No change	COCs do not have a significant adverse effect on sexual function
GROUP D									
Warner and Bancroft, 1988[55]	UK	860	4,112	18+	Retrospective, uncontrolled	Questionnaire	No data	No change	The least variations in libido were seen in women taking a monophasic COC

Martin-Loeches *et al.*, 2003[56]	Spain	760	1,073	31	Prospective, uncontrolled	FSFI	No data	Increase	Sexual desire increase is seen mostly between 6 and 12 months of contraceptive use
Brucker *et al.*, 2010[57]	Nine EU countries	1,665	1,665	18–40	Multicentre, uncontrolled	Quarterly controls, questionnaire, laboratory examinations	No data	No change	The COC containing 20 μg EE/2 mg CMA in 24/4 day regimen does not affect libido
Walwiener *et al.*, 2010[24]	Germany	752	1,219	18–35	Retrospective, uncontrolled	FSFI	No data	Decrease	COC users had lower sexual functioning scores and lower sexual desire
Heskamp and Schramm, 2010[58]	Germany	2,039	2,039	33	Prospective, uncontrolled	Electronic questionnaire	No data	No change	The COC (30 μg EE/2mg CMA) does not negatively affect libido
Totals		*8,422*	*13,673*						

COC, combined oral contraceptive; IRSF, Interviewer Rating of Sexual Function; SES, Sexual Experience Scales; VAS, visual analogue scale; PEQ, Personal Experience Questionnaire; EE, ethinylestradiol; FSFI, Female Sexual Function Index; SDI, Sexual Desire Inventory; BDI and BDI-II, Beck Depression Inventory; SF-36, Short Form-36; SPEQ, Short Personal Experience Questionnaire; CMA, chlormadinone acetate; GSA, Genital Sensory Analysis; SDM, Structured Diagnostic Method; AFSFO, Abbreviated Female Sexual Function Questionnaire; FSFQ, Female Sexual Function Questionnaire; SDI-2, Sexual Desire Inventory-2; DAS, Dyadic Adjustment Scale; SES, Subjective Experience Scale; FSDS-R, Female Sexual Distress Scale-Revised; HSDD, Hypoactive Sexual Desire Disorder; E_2V, oestradiol valerate; DNG, dienogest; MFSQ, McCoy Female Sexuality Questionnaire; DRSP, drospirenone; CPA, cyproterone acetate; SEQ, Side Effect Questionnaire; SDS, Sexual Distress Scale; SHBG, sex hormone binding globulin; WHOQOL, World Health Organisation Quality of Life; DSFI, Derogatis Sexual Function Inventory.

Table 1b Summary of Table 1a.

Impact of COCs on libido (n = 8,422)	*Increase*	*No change*	*Decrease*
Number of COC users	1,826	5,358	1,238
Change in libido (%)	21.7	63.6	14.7
Number of studies	15	12	9
GROUP A			
Number of respondents	398	293	169
Change in libido (%)	46.3	34.1	19.7
GROUP B			
Number of respondents	515	186	317
Change in libido (%)	50.6	18.3	31.1
GROUP C			
Number of respondents	153	315	0
Change in libido (%)	32.7	67.3	0.0
GROUP D			
Number of respondents	760	4,564	752
Change in libido (%)	12.5	75.1	12.4
Impact of COCs on free testosterone levels and libido	*Increase*	*No change*	*Decrease*
Number of studies	8	6	4
Impact of decreased free testosterone on libido (*n* = 846)	*Increase*	*No change*	*Decrease*
Number of COC users	410	261	175
Change in libido (%)	48.5	30.9	20.7
Impact of unaffected free testosterone levels on libido (*n* = 50)	*Increase*	*No change*	*Decrease*
Number of COC users	18	32	0
Change in libido (%)	36.0	64.0	0

(e.g., USA, Canada, Europe, and Asia). The number of respondents in each study varied from 19 to 4,112. The total number of respondents in all studies was 13,673, of which 8,422 respondents were COC users. The smaller studies were more detailed; more general information was provided in larger ones, which also were affected by a smaller statistical error.

COC users reported an increase in sexual desire in 15 studies, no impact on sexual desire in 12 studies, and a decrease in 9 studies. Information was gathered mostly by means of questionnaires (e.g., Interviewer Rating of Sexual Function [IRSF] or Female Sexual Function Index [FSFI]). In almost half of the studies ($n = 18$), sexual desire was correlated with changes in free testosterone and SHBG levels. The results of these studies were relatively heterogeneous and inconsistent, which is mainly due to the variable inputs (age and cultural-ethnic composition of respondents, number of samples, etc.). Ten studies did not provide the exact COC composition, dosage, or dosage regimen (Table 1).

To compare the impact of COCs on sexual desire, the studies were divided into *small* (Group A: up to 100 respondents; 18 studies), *medium* (Group B: 100–299 respondents; ten studies), *large* (Group C: 300–999 respondents; three studies), and *extra large* (Group D: over 1,000 respondents; five studies) (Table 1). The score of sexual appetency (increase/decrease/no change) in each of the groups are: 8/4/6 in Group A, 5/4/1 in Group B, 1/0/2 in Group C, and 1/1/3 in Group D. A greater number of respondents was associated with a greater likelihood for the study to report no change in sexual desire. Of the 36 papers retained only 18 reported on the impact of COCs on free testosterone levels, 15 of which confirmed a decrease in free testosterone levels; in only three studies no change had been observed. The effect of COCs on free testosterone levels was not evaluated in the larger studies.

In Table 2 the different COC formulations, oestrogen and progestin doses, dosage regimen, changes in the levels of free testosterone, and impact of COCs

Table 2a Overview of studies evaluating effect of COC on sexual desire based on oestrogen/progestin doses and regimen.

Author, year	*Oestrogen dose*	*Progestin dose*	*Impact on free testosterone levels*	*Impact on SHBG levels*	*Impact on sexual desire*	*No. of COC users*	*Age (mean and/or range)*
Monophasic COCs							
Caruso *et al.*, 2004[21]	15 μg EE	60 μg gestodene	No data	No data	Decrease	48	18–35
Caruso *et al.*, 2005[26]	30 μg EE	3 mg drospinerone	No data	No data	No change	80	19–31
Guida *et al.*, 2005[31]	20 μg EE	150 μg desogestrel	No data	No data	Increase	25	22–34
Oranratanaphan and	30 μg EE	3 mg drospinerone	Decrease	No data	Increase	42	18–35
Taneepanichskul, 2006[40]	20 μg EE	75 μg gestodene	Decrease	No data	Increase	44	18–35
Sabatini and Cagiano,	20 μg EE	100 μg levonorgestrel	No data	No data	Increase	94	30
2006[53]	15 μg EE	60 μg gestodene	No data	No data	Decrease	92	30
Graham *et al.*, 2007[41]	35 μg EE	0.25 mg norgestimate	Decrease	Increase	No change	7	18–31
Heskamp and	30 μg EE	2 mg CMA	No data	No data	No change	2,039	33
Schramm, 2008[58]							
Skrzypulec and	30 μg EE	3 mg drospinerone	No data	No data	Increase	61	18+
Drosdzol, 2008[54]							
Caruso *et al.*, 2009[43]	30 μg EE	2 mg CMA	Decrease	Increase	Increase	72	18–32
Lee *et al.*, 2010[44]	20 μg EE	No data	Decrease	No data	No change	24	18–35
Strufaldi et al., 2010[45]	30 μg EE	150 μg levonorgestrel	Decrease	Increase	No change	49	28
	20 μg EE	100 μg levonorgestrel	Decrease	Increase	Increase	48	28
Brucker et al., 2010[57]	20 μg EE	2 mg CMA	No data	No data	No change	1,665	18–35
Caruso et al., 2011[27]	20 μg EE	3 mg drospinerone	21/7 - No data	21/7 - No data	Increase	54	18–37
	20 μg EE	3 mg drospinerone	24/4 - No data	24/4 - No data	Increase	61	18–37
Battaglia et al., 2011[48]	30 μg EE	3 mg drospinerone	Decrease	Increase	Decrease	22	18–35
Triphasic COCs							
Graham et al., 2007[41]	25 μg EE	0.18-0.215-0.25 mg norgestimate	Decrease	No change	Increase	30	18–31
	35 μg EE	0.18-0.215-0.25 mg norgestimate	Decrease	No change	Increase	24	18–31
Greco *et al.*, 2007[42]	25 μg EE	0.18-0.215-0.25 mg norgestimate	Decrease	No change	Increase	24	18–30
	35 μg EE	0.18-0.215-0.25 mg norgestimate	Decrease	No change	Increase	24	18–30
Quadriphasic COCs							
Caruso *et al.*, 2011[47]	E_2V	dienogest	Decrease	Increase	Increase	57	33
Total COC users						*4,690*	

COC, combined oral contraceptives; EE, ethinylestradiol; CMA, chlormadinone acetate; E_2V, oestradiol valerate

on libido are summarised. Of the 16 studies concerning pills containing ethinylestradiol as the oestrogen component ($n = 4{,}690$), which are mentioned in the table, 13 focus on monophasic regimens; two on triphasic COCs, and one, on both types. Also included was a study of COCs containing natural oestrogen (E_2V) administered in a quadriphasic regimen, which showed a positive effect on sexual desire[47]. Based on the EE content of the pills concerned, the studies were divided into two groups: low (15–20 μg) and relatively higher EE dosage (25–35 μg). None of the selected articles reported on COCs with 50 μg EE and all were published between 2004 and 2011. In those concerning pills containing 15 to 35 μg EE the number of respondents aged 18 to 37 years varied from 22 to 2,039. One of the papers reported on COCs with 2 to 3 mg E_2V, and dienogest[47]. One study comparing traditional 21/7 and 24/4 cycles of contraceptives with an identical content (20 μg EE, 3 mg drospirenone) showed a favourable effect of the 24/4 cycle on libido[27]. The authors suggested that shortening of the hormone-free interval increases sexual spontaneity. Only in three of the 16 studies (Table 2) focusing on the impact of the oestrogen dose on libido did sexual desire lessen during administration of monophasic COCs: this was observed with pills containing either 15 μg EE and 60 μg gestodene ($p < 0.005$) in groups of 48 and 92 women[21,53] or 30 μg EE and 3 mg drospirenone in a group of 22 COC users[48]. Of the other studies on monophasic contraceptives, an increase in libido was reported in nine studies[27,31,40–43,45,53,54], and no change in six[26,41,44,45,57,58]. Triphasic COCs containing 25 to 35 μg EE and 0.18–0.215–0.25 mg norgestimate caused, in a cohort of 102 women aged 18 to 31 years, free testosterone levels to drop whereas sexual desire changed in neither of the two studies concerned[41,42].

Only 6% of women taking pills with a low EE content ($n = 2{,}212$) reported a drop in sexual desire; 17%, an increase in libido; and 76%, no change. Treatment with COCs containing a relatively higher EE dose ($n = 2{,}478$) was associated with a libido increase in 7%; no change in 92%; and a libido decrease in 1% (Table 2).

DISCUSSION

Findings and interpretation

This systematic review reveals that, in most cases, biologically active testosterone is reduced and SHBG is elevated after COC use, but a clear effect on sexual desire is not confirmed.

Table 2b Summary of Table 2a.

Relatively lower EE dose (15–20 μg)	*Libido Decrease*	*Libido Increase*	*Libido No change*	*Total no. of COC users in lower EE dose group*
Number of COC users	140	383	1,689	2,212
Change in libido (%)	6.3	17.3	76.4	100.0
Relatively higher EE dose (25–35 μg)	*Libido Decrease*	*Libido Increase*	*Libido No change*	*Total no. of COC users in higher EE dose group*
Number of COC users	22	179	2,277	2,478
Change in libido (%)	0.9	7.2	91.9	100.0
Number of COC users per EE dose	*Libido decrease*	*Libido increase*	*Libido no change*	
15 μg	140	0	0	
20 μg	0	383	1,689	
25 μg	0	0	54	
30 μg	22	179	2,168	
35 μg	0	0	55	

The role of androgens in female sexuality is generally accepted, but the mechanisms underlying their effects remain unclear[14,15,42]. Female sexual responses vary considerably, and they are influenced by other hormonal- and by non-hormonal factors. It is assumed that androgens enhance sexual desire and response, but their impact depends on individual sensitivity to free testosterone and a certain 'critical' level of free testosterone in the subnormal range[41,42]. Insufficient androgens have been linked to impaired well-being and HSDD[16,18]. Some studies do not validate a direct connection between androgen reduction and sexual responses[17,41].

Strengths and weaknesses of the study

The strengths of the study are that it is a comprehensive review of studies conducted in this subject area since 1975, and that it provides reliable information on the most relevant study findings regarding the effects of COCs on sexual desire. The main limitation of our systematic review is related to the heterogeneous character of the studies retained with regard to changes in sexual desire, the perception of which is based on the subjective feelings of the respondents. Further, their comparison was complicated by the use of different methods and questionnaires. We focused mainly on the conclusions of the selected studies, even though these conclusions were arrived at by different methods. We could not carry out a standard meta-analysis; instead, we chose the method of synthesis[36] of 36 studies, in which we evaluated whether COCs augmented, reduced, or had no effect on sexual desire.

The effects of COCs on free testosterone levels and libido are analysed in our systematic review. In evaluating serum concentrations of free androgens it is important to consider their variability, which is dependent on the pulsed secretion of gonadotropin-releasing hormone (GnRH), and to be aware that their determination in some cases is affected by technical problems, particularly when androgen levels are low. We did not evaluate the impact of the doses and the androgenicity of progestins contained in COCs because of the limited number of studies and their rather contradictory results.

Studies accepted for inclusion were examined with respect to the involvement of pharmaceutical companies. Almost 25% of accepted studies were identified as having such involvement, the nature of which varied. Support sometimes took the form of financing whereas, in other cases, it consisted of providing COC samples or technical support, such as laboratory assays. The question should be raised whether such support may affect the results. In most papers related to studies supported by the industry no change in libido whilst using COCs is reported, which might be positive information for a pharmaceutical company. We have included in our review one large study with 752 pill users, that was not sponsored by a pharmaceutical firm: the authors concluded that use of the COCs concerned was associated with a decrease in libido[24]. We think that in some supported studies a biased formulation of the questions in questionnaires or personal interviews may cause misrepresented results, but for this we have no evidence. Be that as it may, if we should limit ourselves to examining studies not supported by pharmaceutical companies, we would likely come to similar conclusions.

Differences in results and conclusions in relation to other studies

The findings of studies assessing COC-induced changes in serum levels of androgen and SHBG are mostly similar; the latter consist of a decrease in free testosterone levels[10,21,22,26,39,40–48,52] and, when determined, an increase in SHBG levels[41,43,45,48].

Panzer *et al.* have hypothesised that chronic elevation of SHBG when using the pill can cause long-term sexual problems and that prolonged COC use might induce gene imprinting for elevated SHBG production, which would lead to chronic elevation of SHBG levels even *after* discontinuing intake of the contraceptive[22,59]. In our review the aforementioned hypotheses proved not to be borne out as most studies report no changes in libido neither while taking the pill nor after its discontinuation. According to a study by Bancroft *et al.*, within six months of discontinuation of their pill, 26 former COCs users showed levels of SHGB comparable to those of women who had never taken the pill (previous users $n = 26$, 36 ± 1 nmol/l; non-users $n = 34$, 53.5 ± 28.7 nmol/l; $p = 0.52$); this disproves Panzer and co-authors' theory[60]. Even though Graham *et al.* describe that levels of total testosterone, free testosterone, and dehydroepiandrosterone sulphate are still significantly reduced three months after stopping COC use, sexual interest is not decreased in most

women[41]. We were able to confirm this observation in our review when we took into consideration a sample of 896 respondents, for whom information on free testosterone levels and libido changes was provided. In 80% ($n = 671$) of these subjects, sexual desire was unchanged or increased even though the levels of free testosterone were reduced. Libido decreased in 20% ($n = 175$) of the respondents (Table 1).

In case levels of free testosterone should be directly proportional to the intensity of sexual desire, we would have to assume that women with elevated androgen levels (e.g., those with polycystic ovary syndrome, which affects over 5% of the women)[61] would have higher sexual interest. However, in these women, satisfaction with sexual life is lower than in healthy women; moreover, they have lower sexual self-esteem due to their frequently associated higher body mass index, hirsutism, acne, mood changes, and depression[62,63]. On the contrary, when COCs containing 30 μg EE and 2 mg chlormadinone acetate were used to reduce hyperandrogenicity, sexual desire was reported to have risen among the 72 participants[43].

Similarly, the theory that low androgen levels in COC users contribute to a low libido was questioned in two studies that examined the effects of administering supplemental androgens to COC users. Although women on the supplement displayed significantly higher free testosterone levels, their sexual function was not significantly improved[37,49]. But according to Shifren *et al.*, additional androgen therapy is efficient in the treatment of women with HSDD[64]. It is unknown whether this effect is linked to the conversion of androgens into oestrogen or only to the direct effect of androgen.

Studies on the relationship between oestrogen dose and sexual desire have yielded inconsistent results. Strufaldi *et al.* found that during intake of a pill containing 30 μg EE/150 mg levonorgestrel (LNG), plasma androgen levels decrease but without any negative impact on sexual desire; however, with a lower oestrogen dose (20 μg EE/100 mg LNG), sexual interest augments[45]. Caruso *et al.* found that a lower EE dose (15 μg EE) caused vaginal dryness and a decrease in sexual desire[21]. Sabatini and Cagiano compared two COCs containing either 15 μg or 20 μg EE and concluded that 20 μg EE caused a small increase in sexual desire in almost 47% respondents, while 15 μg EE had a negative impact on sexual interest[53]. Greco *et al.* reported that 25 μg EE decreases free testosterone levels less than 35 μg EE and has a more pronounced positive effect on mood[42]. Battaglia *et al.*[48] observed that COCs containing 30 μg EE and 3 mg drospirenone lessen sexual desire and cause a lubrication disorder, which is in contrast with the findings of Caruso *et al.*[26]. Authors have shown that the different doses of COCs have different effects: 20 μg EE and higher does not have a negative impact on libido, but 15 μg EE in some cases causes a decrease in sexual desire mainly related to vaginal dryness[21]. This is also confirmed by our review, wherein all women on this dose observed a decrease in sexual desire. For COCs containing 20–35 μg EE, there was no change in sexual desire in most women (85%) (Table 2).

McCoy *et al.* did note significantly more frequent sexual thoughts and fantasies in users of a triphasic pill as compared with users of a monophasic one, whereas the only difference in COC composition was a lower dose of progestin in the triphasic regimen[12]. Unlike the aforementioned authors, we did not find any difference between the effects of monophasic and triphasic oral contraceptives on libido. The 24/4-cycle COC regimen had a better effect on sexual desire than the traditional 21/7 cycle[27]. One of the most recent developments is the use of the natural oestrogen E_2 or its valerate, in COCs. E_2V is used in combination with dienogest, a 19-nortestosterone derivative and is claimed to improve sexual desire[47].

Different perceptions of libido changes can be caused by different EE doses in the COCs, but individual observations of sexual desire might as well be misrepresented due to methodological faults in the evaluation of various types of questionnaires, cohort sizes, length of COCs administration, and psychosocial factors. In order to measure sexual responses in an unbiased manner some studies use a device like the vulvagesiometer[44] but this may also result in large individual dispersions. Most studies do not examine the role of the sexual partner, the quality and length of the relationship, and overall wellbeing, which are all indicators subject to great variability, that affect libido as well.

The sexual desire of COC users is also influenced by non-hormonal factors. A decrease in sexual desire is more commonly observed in women with increasing age, multiparity, and a poor partner relationship[56,65]. Some studies point out the important role of a more restrictive sexual morality in different cultural, ethnical, and religious societies[24]. This was verified in a study

concerning the sexual behaviour of women in Scotland and the Philippines[13]. The sexual interest of Scottish women may have declined due to a cultural factor: Scottish women have a higher capability of disclosing their negative feelings than Philippine women. In contrast, Heiman *et al*. do not mention any changes in the sexual behaviour of women in two countries with the same socio-economic background (USA and the Netherlands)[46].

Relevance of the findings: Implications for clinicians

Even though COCs appear to modulate sexual desire in various ways, we cannot define a single indicator reliably and clearly characterising a cause-effect relationship. This is mainly due to the simultaneous and intertwined effects of a variety of complex biological, psychological, social, and multidimensional factors. Androgen level is not the only and, most likely, not even the most important predictor of sexual desire[66,67].

Clinicians, when prescribing a COC, should take into account – beside the risk profile – the patient's medication, her age, and the expected effect of the contraceptive on sexual desire and behaviour. Sexual history taking should form an essential part of the dialogue with such a patient.

CONCLUSION

Although use of COCs is linked to the quality of sexual life, the effect is complex, and there are no means to objectively determine whether sexual desire is influenced. Treatment with a COC causes the serum levels of free testosterone to drop but, in most cases, this does not induce a decline in libido. Most studies and our review are consistent in finding that COCs with an ultra-low oestrogen dose (EE $<$ 20 μg) reduce sexual desire more than those with a higher oestrogen content (EE $\geq$ 20 μg). The latter usually do not alter libido. Changes in free testosterone levels have an impact on sexual desire only when the values decline below a certain level, and those changes are found mainly in women who are more sensitive to such changes. Psychosocial, cultural and other relational factors, as well as personal characteristics, exert the greatest influences on sexual desire. The effect of COCs cannot be clearly defined due to the complex nature of female sexuality and sexual desire. Future studies may increase our knowledge in this domain.

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

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