Does oral contraceptive-induced reduction in free testosterone adversely affect the sexuality and mood of women?

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Abstract:

The aim of this study was to examine whether changes in plasma androgen levels (total testosterone (T), free testosterone (FT), and dehydro-epiandrosterone-sulfate (DHEA-S)) induced by oral contraceptive (OC) use were related to changes in sexual interest or response or in mood. Sixty-one women provided blood samples and were assessed, using interviews and standardized questionnaires, prior to starting, and after 3 months on OCs (Ortho-Tricyclen®, Ortho-Tricyclen-Lo®, or Ortho-Cyclen®, all containing the same progestagen, norgestimate). Significant decreases in T, FT, and DHEA-S were found after 3 months, although the extent of reduction was variable across women. There was some support for a relationship between the degree of reduction in total T and FT and the frequency of sexual thoughts after 3 months on OCs. However, some women had no loss of sexual interest in spite of substantial reduction in FT, and there was overall no evidence that reduction in FT affected enjoyment of sexual activity with a partner. The findings are consistent with the idea that some women may be more sensitive to changes in T than others. No relationship was found between negative mood, as assessed by the Beck Depression Inventory, and changes in T, FT, or DHEA-S.

Keywords: oral contraceptives | testosterone | SHBG | sex | mood | women's health | sexual health

Article:

1. Introduction

Since the introduction of oral contraceptives (OCs), the reported effects on sexuality and mood have been variable, with some women reporting improvement, some worsening and usually a majority reporting no change (Bancroft and Sartorius, 1990; Davis and Castaño, 2004). Negative

changes in mood and sexuality, however, were found to be the strongest predictors of discontinuation in the first 6 months of OC use (Sanders et al., 2001), emphasizing the need to understand the mechanisms underlying these negative effects when they occur.

Although many non-hormonal factors will influence a woman's reaction to OCs, there is some evidence that direct hormonal effects are relevant (Cullberg, 1972; Graham et al., 1995). Moreover, despite a strong association between well-being and sexual desire in OC users (Warner and Bancroft, 1988), and women in general (Bancroft et al., 2003), there is also some placebo-controlled evidence that negative effects of the pill on mood do not account for the negative effects on sexuality (Leeton et al., 1978; Graham and Sherwin, 1993), and need to be considered separately.

It has been known for some time that OCs lower free testosterone (FT), partly because of suppression of ovarian steroid production and partly because of increased sex hormone binding globulin (SHBG), which results in a reduction in unbound or FT (Jung-Hoffman and Kuhl, 1987; Van der Vange et al., 1990; Janaud et al., 1992; Darney, 1995; Thorneycroft et al., 1999; Boyd et al., 2001). There is more limited evidence of a reduction in dehydro-epiandrosterone-sulfate (DHEA) and its sulfate (DHEA-S) (Coenen et al., 1996). The possibility that such hormonal changes might be related to mood or sexual negative side effects of OCs has been acknowledged (Bancroft and Sartorius, 1990; Davis and Castaño, 2004), but has received little research attention.

At the present time there is considerable interest in the role of androgens in both the sexuality and well-being of women, with claims that testosterone (T) deficiency is an important cause of hypoactive sexual desire in women (e.g., Guay et al., 2004), and evidence that DHEA administration is effective in treating depression in men and women (Schmidt et al., 2005). The evidence of a role for T in the sexuality of women is, however, inconsistent (for review, see Bancroft, 2003). In a recent large-scale community-based survey of 1021 women aged 18–75 years, Davis et al. (2005) found no association between the presence of sexual problems and low total or free T or androstenedione. Some association was found with low DHEA-S in pre-menopausal women, although the majority of women with low DHEA-S did not report sexual problems. In the same study, however, an association between DHEA-S and well-being was found in premenopausal women (Bell et al., 2006). Ovaries are an important source of androgens in both pre- and postmenopausal women, and oophorectomy substantially lowers androgen levels (Judd et al., 1974). However, Nathorst-Böös et al. (1993) found that only 50% of women reported sexual problems following this procedure, suggesting that many women can experience substantial reduction in androgens without adverse sexual effects. On the other hand, in those women who experience such problems following oophorectomy, exogenous testosterone

administration has been shown to be beneficial in placebo-controlled studies (e.g. Sherwin et al., 1985; Shifren et al., 2000). A reasonable conclusion from this inconsistent evidence is that T has an enhancing effect on sexuality at least in some women.

The commonest iatrogenic cause of lowered T in women is OC use. However, no studies have investigated whether there is a relationship between the reduction in T and changes in sexual interest or response or mood in women after starting on OCs. Furthermore, the limited evidence correlating T levels with mood or sexuality in women on OCs is restricted to women established on the pill; those who develop adverse effects are likely to have discontinued OC use, or at least switched to a different OC. It is noteworthy, however, that correlations between T and sexual interest have been more evident in women established on OCs than in non-OC users (Bancroft et al., 1980 and Bancroft et al., 1991; Alexander and Sherwin, 1993). This raises the interesting possibility, suggested by Alexander and Sherwin (1993), that the impact of varying T levels on women's sexuality will only be apparent when they are close to or below a certain threshold. This could explain why correlations between T and sexuality are observed in women taking OCs, if the T is reduced to levels around this threshold. In men, it is only when levels of T fall below a certain critical threshold (much higher than the top of the physiological range in women) that one sees clear correlations between T levels and sexual interest (Bancroft, 2003). However, the possibility of a low critical T threshold in women is difficult to reconcile with the clear evidence that supra-physiological levels of T following testosterone administration have beneficial sexual effects, with symptoms returning when levels have fallen but are still in the supra-physiological range, to an extent not evident in men (for review, see Bancroft, 2003). An additional complicating factor is that psychological problems might serve to obscure relatively subtle hormone–behavior relationships. One early study (Bancroft et al., 1980) compared 20 OC users complaining of low sexual desire, which they attributed to OC use, to 20 OC users without sexual problems. The levels of total T and SHBG were very similar in the two groups (FT was not estimated), but a correlation between T levels and sexual interest was only observed in the non-problem group.

In this paper, we report the first study to measure changes in total T, FT, SHBG, and DHEA-S as well as mood and sexuality, in women starting on OCs. In view of the evidence cited above, we tested two hypotheses, both based on the assumption that androgens are relevant to OC-induced negative changes in sexuality and mood. The first postulates that it is the amount of reduction in T or DHEA-S that is relevant; women who experience loss of sexual interest or response, or worsening of mood, will show greater reduction in androgens than those with no negative or with positive changes on OCs. The second hypothesis, restricted to sexual effects, was based on the ‘threshold’ possibility, discussed above. We predicted that levels of sexual interest or response will be affected when T or FT levels fall below a certain level. OCs, by substantially lowering T

and FT levels, may effectively lower levels to below the threshold for some women. The specific prediction here is that relationships between T level and sexuality will become more apparent by looking at actual T levels after OC-induced reduction, rather than the amount of reduction from pre-OC levels.

2. Methods

2.1. Recruitment

There were two sources of recruitment: the main study and a sub-sample from an earlier study (Study 2). The main study was carried out in 2003–2004 and involved women starting on OCs, with random assignment to either Ortho-Tricyclen® (OTC) or Ortho-Tricyclen-Lo® (OTC-Lo). Both OTC and OTC-Lo have the same triphasic regime of progestagen (norgestimate 0.18, 0.215 and 0.25 mg), but different levels of EE (OTC: 35 μg EE; OTC-Lo: 25 μg EE). The comparison of these two OC formulations will be reported in a separate paper (Greco et al., unpublished data). The principal aim of Study 2, carried out in 1998–1999, was to investigate predictors of early discontinuation of OC use and the main findings were reported by Sanders et al. (2001). A sub-group from this study (n=13) also provided blood samples during the pre-OC baseline month, and again during the 3rd month on OC. Due to problems with recruitment, this sub-sample remained too small for separate analysis. Because the methods of recruitment and behavioral assessment were very similar in the two studies, these two samples have been combined for the analysis presented in this paper. Women in Study 2 had been randomly assigned to OTC or Ortho-Cyclen, a monophasic version with the same progestagen (0.250 mg norgestimate) and dose of EE as OTC.

Recruitment to Study 1 was via advertisements posted at an Indiana University Health Center, the local Planned Parenthood Clinic, the campus newspaper and the Kinsey Institute website. For Study 2, recruitment was through the same University Health Center and Planned Parenthood Clinic. Inclusion criteria were 18 years of age or older, in a heterosexual relationship of at least 3 months duration, and intending to use OCs for birth control for at least 3 months (1 year in Study 2). Participants were also required to be university students as the blood sampling and medical screening took place at the University Health Center. Other inclusion criteria included: (1) menstrual cycle length of 21–35 days; (2) no history of diabetes or hypertension; (3) no current use of psychotropic medications, anti-neuroleptics, or daily antibiotics; (4) no current breast feeding; and (5) no pregnancy within the last 6 months. Women who had used OCs within the past 3 months (6 months for Study 2) or had known contraindications to OC use were excluded from the study. In the main study, participants received $60 for the initial interview and an additional $60 for the follow-up assessment, together with a free 3 months supply of OC. In Study 2, $50 was paid for the first assessment and $20 for each subsequent assessment. The

Indiana University Institutional Review Board approved both studies and informed consent was obtained from all participants.

In the main study, of the 106 women who were screened, 23 were ineligible, 23 were eligible but did not agree to participate, and 60 were enrolled in the study. While full follow-up data are given in the Results section, 48 of these 60 women provided data at the follow-up assessment, with blood samples being provided by 47. In Study 2, 107 women started, of whom 26 were lost to follow up and two became pregnant, leaving 79 women who were followed up for 12 months or who were assessed at earlier discontinuation. Thirteen of these women were in the sub-group involving blood sampling and were included in this report. The total sample size was thus 61 women (48 from Study 1 and 13 from Study 2). This size of sample was considered acceptable since it would give 80% power at two-sided $p<0.05$ to detect a moderate correlation coefficient of 0.3 and, comparing two groups of 30 women each, a moderate/large effect size of 0.75 and a 33% difference in proportions.

Women were assessed prior to starting the OC and again after 3 months of OC use. For randomization, a computer-generated random sequence of numbers was used, with odd numbers assigned to one pill group and even numbers to the other. The randomization list was kept by a member of the research team (J.B.) who had no contact with any of the participants. As stated above, assessment was very similar in the two studies, but there were two differences, one involving assessment of sexuality, and the other, blood sampling. These will be explained below.

2.2. Behavioral assessment

After providing informed consent, study participants were interviewed and completed questionnaires before starting the OC. This assessment was repeated after three months of OC use; unless otherwise noted, all of the measures below were used in both Studies 1 and 2.

2.2.1. Completed at initial assessment only

2.2.1.1. Demographic and relationship questionnaire (DRQ)

This self-report questionnaire obtained demographic information concerning age, employment status, marital status, education, racial/ethnic background, and income. It also assessed relationship status and commitment by asking about sexual exclusivity, length of relationship, and time spent together.

2.2.2. Completed pre-OC and repeated after three months on OC

2.2.2.1. Beck Depression Inventory (BDI)

This well-validated instrument for measuring severity of depressive symptoms during the preceding week has 21 items, each of which is rated absent (0) to severe (3), with a total score range of 0–63. Scores from 0–9 are considered minimal, 10–16 mild, 17–29 moderate, and 30–63 severe depression (Beck and Steer, 2000). Due to possible variation of mood through the menstrual cycle each woman completed the BDI on the first day of bleeding, to cover the premenstrual week and start of menses.

2.2.2.2. Interviewer ratings of sexual function (IRSF)

This is a semi-structured interview that has been used in a number of studies (Tyrer et al., 1983; Graham et al., 1995; Sanders et al., 2001) and has shown good inter-rater reliability. The IRSF was used to establish the frequency, over the preceding 3 months, of different types of partnered sexual activity as well as masturbation and, as a measure of sexual interest, of sexual thoughts. The question about frequency of sexual thoughts, our principal measure of sexual interest, was as follows: “Apart from the times that your partner approached you wanting to make love, how often have you found yourself thinking about sex with interest or desire?” The response categories for frequency are shown in Table 2. The IRSF also established the proportion of sexual acts with the partner during the 3 month period that were: initiated by the woman, experienced as pleasurable and enjoyable, associated with sexual excitement or arousal, and associated with orgasm (and various other aspects not reported in this paper). These proportions were rated on a six-point scale (0=never; 1=<25%; 2=about 25%; 3=about 50%; 4=about 75%; and 5=most or all occasions).

An additional measure of sexual interest, the Sexual Desire Inventory (SDI-2) (Spector et al., 1996) was used in the main study but not in Study 2. The SDI-2 measures two aspects of sexual interest: “Dyadic desire” (interest in sexual activity with another person) and “Solitary desire” (interest in engaging in sexual behavior by oneself e.g., masturbation). The correlations between the SDI and the IRSF for the main sample are presented here as they provide some evidence for convergent validity of the IRSF. The SDI Dyadic score correlated with the IRSF frequency of sexual thoughts, Spearman's correlation coefficient, $r_s=0.58$, ($n=48$, $p<0.001$). The SDI Solitary score correlated with the IRSF-established frequency of masturbation, $r_s=0.91$ ($n=47$, $p<0.001$). As participants in Study 2 did not complete the SDI, no further SDI data are reported in this paper.

2.2.2.3. Side Effects Questionnaire (SEQ)

This interviewer-administered assessment used in previous studies (Graham et al., 1995; Sanders et al., 2001) included a list of 18 items presented to the participant. Both direction (positive or negative) and extent of change (0, none; 1, mild; 2, moderate; and 3, marked) were recorded for each item. Positive scores could reflect reduction in a negative symptom (e.g., menstrual pain) or increase in a positive experience (e.g., increased sexual interest). Following the procedure used by Sanders et al. (2001), three mean summary scores were calculated for positive and negative changes; physical (headaches, feeling bloated, tender breasts, weight gain, nausea, aches and pains, skin changes, abdominal cramps, and tiredness); emotional (feeling better in mood, feeling worse in mood, more emotional, and less emotional); and sexual (loss of sexual interest, increased sexual interest, loss of sexual enjoyment, increased sexual enjoyment, and lack of vaginal lubrication).

2.3. Hormonal assessment

In Study 1, blood samples were taken ±2 days around ovulation in the last pre-OC cycle (based on their usual cycle length), and around pill days 12–14 during the third cycle of OC use. Each sample was assayed for total T, SHBG, % FT, FT and DHEA-S. In Study 2, four blood samples were taken at weekly intervals during the pre-OC cycle and again during the third OC cycle. All four blood samples for each cycle were assayed and means of the week 2 and week 3 samples for each woman for the pre-OC cycle (i.e., the two samples closest to ovulation) and for the third OC cycle were used in the analyses in this paper.

Total T was measured with a Spectria Testosterone RIA kit obtained from Orion Diagnostica (Oulunsalo, Finland). Assay performance was monitored using control samples provided with the kit, and was within limits reported by the kit manufacturer. Assays were carried out in the laboratory of Professor Geoffrey Hammond who had previously published a study of women on OCs using the same direct RIA for total T, which had been validated by comparison with RIA preceded by chromatography (Hammond et al., 2003).

Samples were analyzed in duplicate. If duplicate measurement exceeded 10% of the mean, samples were reanalyzed to ensure accuracy of measurement.

SHBG concentrations were determined using a time-resolved immunoassay kit (PerkinElmer Life Sciences). Assay performance was monitored by inclusion of control samples provided by the kit manufacturer, and inter-assay variability for low and high SHBG concentration controls was within limits reported by the manufacturer. Values are expressed in nmol/L based on standards calibrated in terms of their steroid-binding capacity by Scatchard analysis. Samples were analyzed in duplicate at a 1:200 dilution. Samples containing very high concentrations of SHBG were re-analyzed at a 1:400 dilution to ensure accuracy of measurement.

FT was calculated from a nomogram constructed using serum SHBG concentrations, and the percentage (%) FT measured by centrifugal ultra-filtration dialysis, in serum samples taken from normal female volunteers during treatment with OCs and untreated women during follicular and luteal phases of the menstrual cycle (methods and dataset reported in Hammond et al., 2003). The nomogram allows % FT to be predicted from SHBG values, and this value is then used to determine FT levels from total T measurements.

Serum concentrations of DHEA-S were determined using a commercially available ELISA kit, based on a competitive immunoassay in which DHEA-S in the sample or in standards, competes with a DHEA-S-HRP conjugate for binding to anti-DHEA-S antibodies immobilized in the wells of a micro-titer well plate (Alpha Diagnostic International, San Antonio, TX, USA). The assay has been validated for human serum samples by the supplier, with intra-assay and inter-assay variabilities (% CV) of less than 12% over a wide range of values.

2.4. Statistical methods

Data were entered into Excel and transferred to Statistical Package for the Social Sciences (SPSS) version 13.0 (SPSS Inc, Chicago, Ill, USA) for statistical analysis. Categorical data are presented as N (%), and continuous data as mean (SD). Continuous data were categorized where appropriate so as to explore trends in the data and assess the linearity of any associations. To compare scores between the study groups, chi-squared ($\chi 2$) tests were used for categorical data and Mann–Whitney tests for continuous data. To compare scores over time, Wilcoxon matched pairs signed ranks tests were used. Associations between variables were assessed using the non-parametric Spearman's correlation coefficient (rs). Statistical significance was taken at $p<0.05$ throughout. However, because of the likelihood of Type 1 errors from multiple significance tests, 95% confidence intervals (CIs) are used to express the uncertainty around the estimates.

Nevertheless, with the number of correlations carried out, we cannot exclude the possibility that significance at the 5% level could have occurred by chance.

3. Results

3.1. Participants

Of the 60 women who were recruited into Study 1, 12 (20%) (7 on OTC and 5 on OTC-Lo) did not complete the study. Four of these women were lost to follow-up (2 OTC, 2 OTC-Lo) and eight women discontinued. The reasons women gave for discontinuing were: lack of time (n=1; OTC); side effects (n=4; 2 OTC, 2 OTC-Lo); relationship ended (n=1; OTC); became pregnant (n=1; OTC-Lo); wanted to conceive (n=1; OTC). Combined with the 13 participants from Study 2, this provided a sample of 61 for analysis in this paper. Characteristics of the participants and whether OCs had been used in the past are given in Table 1. Of the 61 participants, 30 women were assigned to OTC (24 in the main study, 6 in Study 2), 24 to OTC-Lo (all in the main study), and 7 to Ortho-Cyclen (all in Study 2).

Table 1.

Sample characteristics (*n*=61); values are given as *n* (%).

Demographic/background variable	Statistic
Age in years, mean (SD)	20.1 (2.3)
Range	18–31
Race	
White	49 (80.7)
Asian	3 (5.3)
Black or African American	3 (5.3)
Other minorities	5 (8.7)
Marital status	
Single/never married	53 (86.9)
Living with partner, but not married	5 (8.2)
Married	3 (4.9)

Demographic/background variable	Statistic
Median length of relationship (months)	11.5
Range	3–182
First time OC user	34 (56.7)

 Due to missing data, *n*=60.

There were no statistically significant differences in demographic characteristics between the participants in the two studies. The analyses were repeated excluding the 13 women recruited in the earlier study; the results were no different from the results in the whole sample.

3.2. Descriptive data on behavioral variables

3.2.1. Sexuality variables

The IRSF ratings of frequency of sexual thoughts for the 3 months prior to starting the OC (Pre) and for the first 3 months on the OC (Post) are shown in Table 2. Although the proportion of women in each of the categories is similar for the two assessments and there were no significant differences between the frequencies at the two assessments, there was considerable individual variability, with 26 women (43%) reporting no change, 14 women (23%) reporting a decrease, and 20 women (33%) an increase in frequency of sexual thoughts (sexual interest).

Table 2.

Interviewer Ratings of Sexual Function (IRSF) before starting on OCs (pre), and after 3 months of OC use (post) (*n*=61).

IRSF	Pre *n* (%)	Post *n* (%)	*n* increased	*n* decreased
Frequency of sexual thoughts			20	14
Absent/rare	0 (0)	2 (3.3)		
1–3 times/month	9 (14.7)	7 (11.7)		
At least once a week	11 (18.0)	7 (11.7)		
Several times a week	27 (44.3)	26 (43.3)		
At least once a day	14 (23.0)	18 (30.0)		
Frequency of sexual intercourse			12	16

IRSF	Pre *n* (%)	Post *n* (%)	*n* increased	*n* decreased
None in previous 3 months	4 (6.6)	1 (1.6)		
1–3 times/month	5 (8.2)	3 (4.9)		
Once a week	5 (8.2)	16 (26.2)		
2–3 times/week	35 (57.4)	32 (52.5)		
4 or>times/week	12 (19.7)	9 (14.8)		

 Due to missing data, the *n* varied from 58 to 61.

The IRSF ratings for frequency of sexual intercourse for the 3 months pre-OC (Pre) and the 3 months of OC use (Post) are also shown in Table 2. Although the largest proportion of women showed no change from Pre to Post-OC, and there was no significant difference between the two assessments, once again there was considerable individual variability, with 16 women reporting a decrease and 12 an increase in frequency of intercourse. The IRSF ratings for other aspects of the woman's sexual experience (e.g., initiation, sexual enjoyment, sexual arousal) and the frequency of masturbation showed similar variability (not shown in Table 2).

3.2.2. Mood

The mean BDI score before starting on OCs was 9.3 (SD 6.8) and after 3 months on OCs was 8.1 (SD 7.4). There were missing data for two women at baseline. Although group mean scores showed a slight improvement (reduction in BDI), there was considerable individual variation and no significant improvement (Mann–Whitney $z=1.35$, $p=0.18$). Taking change scores from −1 to +1 as indicating no change, 19 women (32%) fell in this category; 23 women (39%) showed improvement in mood (reduction in BDI score) and 17 women (29%) worsening in mood.

In summary, for both sexuality and mood measures the comparison of the group mean pre–post assessments suggested little change; however, substantial proportions of women showed increases or decreases.

3.2.3. Side effects

Scores for each of the three summary scores (“physical”, “emotional”, “sexual”; see Section 2 for items) were computed, indicating negative change, positive change, or no change from the pre-OC assessment (see Table 3). These data again highlight the marked variability in women's

responses e.g., for sexual side effects, equal proportions of women showed positive, negative, or no change after starting OCs.

Table 3.

Proportion of women reporting negative change, positive change, or no change in physical, emotional, and sexual summary scores on the Side Effects Questionnaire (SEQ) (*n*=60); values are given as *n* (%).

	Negative change	Positive change	No change
Physical[]	31 (51.7)	21 (35.0)	8 (13.3)
Emotional	24 (40.0)	17 (28.3)	19 (31.7)
Sexual	20 (33.3)	20 (33.3)	20 (33.3)

[] For list of items included in each summary score, see description of SEQ in Section 2.

3.3. Hormone levels

Levels of total T (nmol/L), % FT, FT (pmol/L), SHBG (nmol/L), and DHEA-S (mmol/L) pre and post, and the amount of change pre–post for each hormone parameter, are shown in Table 4. There was a highly statistically significant change in each parameter (all<0.001). While the majority of women showed a decrease in total T, four showed no change and 12 an increase. With FT, all but three women showed a decrease, and with SHBG, all but one woman showed an increase. For DHEA-S, levels decreased in all but 10 women. Spearman's correlation coefficients between change in DHEA-S and changes in total T and FT were rs=0.12, p=0.34, and rs=0.27, p=0.035, respectively.

Table 4.

Serum concentrations of total testosterone (T), percentage of free testosterone (%FT), free testosterone (FT), sex hormone binding globulin (SHBG), and dehydro-epiandrosterone-sulphate (DHEA-S) before starting on OCs (pre), after 3 months of OC use (post), and pre‑post change; values are given as mean (SD) and range.

Serum variable	Pre	Post	Pre–post change	95% CI[]	$p^{\dagger}$
T (nmol/L)	1.21 (0.76)	0.75 (0.86)	0.46 (0.98)	0.21, 0.71	<0.001
Range	0.1–3.7	0.1–6.0	−3.2–3.3		
% FT	2.45 (0.92)	0.78 (0.48)	1.67 (0.91)	1.43, 1.90	<0.001

Serum variable	Pre	Post	Pre–post change	95% CI‡	$p^{\dagger}$
Range	0.63–4.4	0.58–3.4	−3.5–0.22		
FT (pmol/L)	30.77 (28.6)	6.32 (10.4)	24.50 (28.75)	17.01, 31.89	<0.001
Range	3.4–161.7	1.2–64.2	−157.0–8.58		
SHBG (nmol/L)	55.47 (31.8)	235.18 (104.8)	−179.71 (92.1)	−203.50, −155.92	<0.001
Range	17–200	41.5–542	−2.0–484.0		
DHEA-S (mmol/L)	6.98 (3.51)	5.24 (3.00)	1.74 (2.74)	1.03, 2.44	< 0.001
Range	1.52–17.0	0.95–15.20	−8.79–9.15		

‡ CI=confidence interval.

† *p*-value for Wilcoxon signed-ranks test.

SHBG levels at baseline were compared for previous OC users (n=26) and never users (n=34) and were 58.9±36.1 and 53.5±28.7 nmol/l, respectively (t=0.64, p=0.52).

Hypothesis 1. Adverse changes in sexuality will be positively related to the degree of reduction in T after starting OCs.

We tested this hypothesis in two ways, one method incorporating change in the hormonal and behavioral variables from baseline, and the other utilizing the post levels of the sexuality and mood variables.

For each of the mood and sexuality variables, women were divided into two groups: (1) negative change and (2) no change/positive change. For each variable the two groups were compared for degree of change in total T and FT. As shown in Table 5, reductions in total T and FT were not significantly greater in group 1 for any of the sexuality variables, for the BDI, or for the SEQ sexual side effects summary score.

Table 5.

Comparison of change in total testosterone (T), free testosterone (FT), and dehydro-epiandrosterone-sulphate (DHEA-S) in women reporting either negative change or no change/positive change in selected mood and sexuality variables; values are given as mean (SD).

Variable	Negative change	No change/positive change	p
Frequency of sexual thoughts	n=13	n=47[†]	
T change (nmol/L)	−0.754 (0.96)	−0.283 (0.92)	0.17
FT change (pmol/L)	−32.7 (40.6)	−22.2 (24.7)	0.19
DHEA-S change (mmol/L)	−1.80 (2.10)	−1.72 (2.91)	0.96
% of occasions “self” initiated	n=14	n=41	
T change (nmol/L)	−0.626 (0.50)	−0.033 (1.09)	0.08
FT change (pmol/L)	−21.1 (17.2)	−26.9 (33.0)	0.95
DHEA-S change (mmol/L)	−1.67 (4.40)	−1.88 (2.12)	0.67
% of occasions pleasurable/enjoyable	n=9	n=48	
T change (nmol/L)	−0.217 (0.29)	−0.437 (1.05)	0.42
FT change (pmol/L)	−15.2 (13.3)	−27.0 (31.5)	0.40
DHEA-S change (mmol/L)	−1.91 (3.20)	−1.78 (2.77)	0.94
% of occasions aroused/excited	n=15	n=41	
T change (nmol/L)	−0.320 (0.78)	−0.432 (1.04)	0.33
FT change (pmol/L)	−31.1 (28.6)	−22.9 (30.0)	0.13
DHEA-S change (mmol/L)	−1.78 (2.31)	−1.81 (3.00)	0.85
BDI score	n=22	n=36	
T change (nmol/L)	−0.452 (1.02)	−0.374 (0.93)	0.99
FT change (pmol/L)	−32.8 (40.9)	−19.7 (17.8)	0.55
DHEA-S change (mmol/L)	−1.47 (2.82)	−1.89 (2.74)	0.71
SEQ sexual summary score	n=19	n=41	

Variable	Negative change	No change/positive change	p
T change (nmol/L)	−0.545 (0.90)	−0.311 (0.97)	0.87
FT change (pmol/L)	−27.4 (32.1)	−23.1 (27.4)	0.99
DHEA-S change (mmol/L)	−1.41 (2.21)	−1.89 (2.96)	0.46

 p-value for Mann–Whitney test.

† Due to missing data, the n varied from 56 to 60.

With the second approach, the relationships between changes in total T, FT, and DHEA-S and the post levels of mood and sexuality were examined. As Table 6 shows, there was a significant correlation between frequency of sexual thoughts and changes in total T (p=0.02) and FT (p=0.006) and between percentage of occasions sexually aroused/excited and FT (p=0.03) but no other significant correlations with any of the other behavioral variables (only a subset of these are shown in Table 6). There were also no significant correlations between DHEA-S and any of the sexuality or mood variables.

Table 6.

Summary of correlations between changes in hormonal parameters and Post scores on selected mood and sexuality variables three months after starting Ocs.

Variable	r_s	p
Frequency of sexual thoughts		
T† change	0.295	0.02
FT‡ change	0.355	0.006
DHEA-S change	−0.041	0.76
% occasions “self” initiated		
T change	0.249	0.06
FT change	0.008	0.95
DHEA-S change	−0.047	0.73
% occasions aroused/excited		
T change	0.004	0.98

Variable	r_s	p
FT change	0.277	0.03
DHEA-S change	0.033	0.81
BDI		
T change	−0.098	0.46
FT change	−0.126	0.34
DHEA-S change	0.128	0.33

 Due to missing data, the *n* varied from 59 to 61.

† T=total testosterone.

‡ FT=free testosterone.

There was therefore some support for Hypothesis 1, suggesting a relationship between the degree of change in total T and FT and the frequency of sexual thoughts, and the degree of change in FT and sexual arousal/excitement, 3 months after starting on OCs. In addition, the correlation between change in total T and the proportion of occasions that were “self”-initiated was close to significant (p=0.06).

Hypothesis 2. Relationships between T level and sexual interest will become more apparent when androgen levels fall below a certain “critical” threshold.

This hypothesis was tested in two ways. Firstly, we examined the relationship between T levels and our measure of sexual interest at baseline (pre-OC) and after 3 months on OCs (post). If Hypothesis 2 is correct, there should be a stronger relationship between T levels and sexual interest when total T and FT levels are reduced (post) than before women have started on OCs.

There were no significant correlations between total T or FT and sexual interest at baseline (frequency of sexual thoughts and total T, rs=−0.020; frequency of sexual thoughts and FT, rs=−0.072). After 3 months on OCs, correlations between total T and FT and frequency of sexual thoughts were slightly higher (total T, rs=0.143, p=0.28; FT, rs=0.130, p=0.33) but still not significant.

In a second approach, we divided participants into three equal-sized groups based on their FT levels 3 months after starting OCs (post) as follows: low<2.19 pmol/L; medium=2.19–4.72 pmol/L; high>4.72 pmol/L). Table 7 presents cross-tabulations of these three groups with IRSF ratings (post scores). After 3 months on the pill, the majority of women (n=44, 73.6%) reported thinking about sex at least several times a week (reported by n=40, 66.7% at baseline); however, of those who thought about sex less often than this, more (n=13, 81.2%) were in the “low” or “medium” FT groups than in the “high” FT group (n=3, 18.8%) ($\chi 2$=1.42, p=0.234). Similarly, there was a trend for the women who had initiated sex on 50% or more of the times that they had sexual activity with a partner to be progressively more likely to have higher FT scores ($\chi 2$ for linear trend=2.86, p=0.09). Of those women who initiated sex on 25% or fewer of the times that they had sexual activity with a partner, 73.7% (n=28) were in the “low” or “medium” FT group vs. only 26.3% (n=10) in the “high” FT group ($\chi 2$=1.32, p=0.251). For the variable “proportion of occasions sexually excited/aroused”, however, the association was in the reverse direction: women who reported a higher frequency of sexual acts in which they felt sexually aroused were more likely to be in the “low” or “medium” groups (n=37, 74.0%) than in the “high” FT group (n=13, 26.0%) (Fisher's exact test p=0.025). There was a significant linear trend among those who reported being sexually excited/aroused on 75% or more of occasions for them to be progressively less likely to be in the higher FT groups ($\chi 2$ for linear trend=5.18, p=0.023). There were no significant associations found for any of the other IRSF variables (frequency of sexual thoughts, proportion of occasions pleasurable/enjoyable, experienced orgasm, and frequency of masturbation).

Table 7.

Cross-tabulation of level of free T (FT) 3 months after starting OCs (low, medium, and high FT groups) by frequency of the IRSF variables sexual thoughts (post), initiation of sexual activity, and occasions sexually excited/aroused; values are given as *n* (% within FT group).

	FT Group		
	Low (*n*=20)	Medium (*n*=20)	High (*n*=20)
Frequency of sexual thoughts[†]			
Once/month or less	0 (0)	4 (21)	1 (5)
1–4 times/month	5 (25)	4 (21)	2 (10)
Several times a week” to “at least once a day”	15 (75)	11 (58)	17 (85)
Initiation of sexual activity[‡]			

	FT Group		
	Low (*n*=20)	Medium (*n*=20)	High (*n*=20)
⩽ 25% of occasions	15 (79)	13 (65)	10 (53)
⩾ 50% of occasions	4 (21)	7 (35)	9 (47)
Occasions sexually excited/aroused[§]			
⩽ 50% of occasions	1 (5)	2 (10)	6 (32)
⩾ 75% of occasions	19 (95)	18 (90)	13 (68)

 Low=< 2.19 pmol/L; medium=2.19 – 4.72 pmol/L; high>4.7 pmol/L.

† Kruskal–Wallis $\chi^2(2)$, 4.30, p=0.117; mean rank: low 31.25, medium 24.95, high 33.55.

‡ χ^2 (1) for linear trend=2.86, p=0.091.

§ χ^2 (1) for linear trend=5.18, p=0.023.

In summary, we find limited support for Hypothesis 2. Frequency of sexual thoughts and self-initiation of sexual activity with partners was lower in women who were in the “low” and “medium” FT groups. However, it was apparent that some women had a substantial reduction in FT but still experienced reasonable levels of sexual interest.

4. Discussion

Although reduced levels of FT have often been cited as the likely mechanism by which OCs might reduce sexual interest (Davis and Castaño, 2004), this is the first study that has systematically assessed mood and sexual functioning in women before starting on OCs and examined the relationship between OC-induced changes in T and negative behavioral effects. Consistent with previous research (Coenen et al., 1996), mean serum levels of total T, FT, and DHEA-S decreased significantly and levels of SHBG increased in women after starting on OCs, although the extent of the reduction was variable. As our sample included women who had previously used OCs (43.3%) as well as first-time users, we were able to compare SHBG levels in these two groups at baseline (i.e., pre OC use). In contrast with a recent report of persistently elevated SHBG levels in women who had discontinued OC use (Panzer et al., 2006), the SHBG levels of women who were previous OC users and the “never user” group did not differ.

The primary aim of this study was to look at whether changes in androgen parameters from baseline to 3 months of OC use were related to changes in sexual interest or response. We found some support for our first hypothesis, that negative changes in sexuality and/or mood would be related to the reduction in total T and FT after starting OCs and this was only evident from our measures of sexual interest (the frequency of sexual thoughts), and sexual arousal (the frequency of feeling aroused/excited during sexual activity) reported by women 3 months after starting OCs. There was no evidence of T reduction affecting enjoyment of sexual activity with a partner. There was also no relationship between negative mood and changes in T, FT, or DHEA-S.

There was limited evidence for our second hypothesis, that relationships between T levels and sexual behavior would become more pronounced when levels of T are reduced below a certain critical threshold. Low frequency of sexual thoughts and self-initiation of sexual activity with a partner was more likely in women who were at the lower end of the range in FT levels. However, in so far as we found an adverse sexual effect of reduced T levels in women taking OCs, this was only relevant to sexual interest and not to the woman's sexual response and enjoyment during sexual activity with a partner. This would be consistent with the idea that androgens in women primarily affect sexual “motivation” and not response during sexual activity such as arousal and orgasm (Sherwin et al., 1985). It is also important to keep in mind that psychological and relationship factors will interact with possible hormonal mechanisms in influencing a woman's response to starting OCs.

Although the mean ratings on mood and sexuality measures pre-post OC suggested very little change, this obscured the fact that for all measures, in addition to a subgroup showing no change, similar proportions of women showed either positive or negative changes. Without a placebo control, it is difficult to know to what extent such variability would occur over a 3-month period even if women were not using hormonal contraception. However, it is noteworthy that even in controlled studies, this pattern of marked variability in response to OCs has been recognized for some time (Cullberg, 1972; Bancroft and Sartorius, 1990). In fact, the most consistent finding in the literature addressing the impact of OCs on mood and sexual interest has been the marked variability in women's responses to the pill.

It is clear that substantial reduction in FT can occur in many women without impairment of sexual interest or response. It remains possible, however, that such reduction could have an impact in a minority of women who are more sensitive to the behavioral effects of T. Given that we have no idea what proportion of women would come into our postulated category of “testosterone sensitive”, if indeed such a category exists, there is a need to identify predictors or markers of such T sensitivity. Unfortunately, the sample size in this study was too small for this

purpose. Limited attention has been paid to predictors of negative mood change. Early studies suggested that women who had a previous history of depression might be more likely to become depressed after starting on OCs (Lewis and Hoghughi, 1969). Cullberg (1972), in a study comparing differing progestagen doses, found that women with a history of premenstrual irritability had more negative reactions when taking “low-progestagen” OCs. Bancroft et al. (1987) randomly assigned women to either a combined or a triphasic OC. In women with high premenstrual mood change before starting the pill, those who took the triphasic OC showed significantly lower mood and “sexual feelings” than those who took the combined pill. Another possible marker of T sensitivity that would merit investigation is the experience of higher sexual interest around ovulation, when T levels increase. Future research involving larger samples of women and assessment of a wide range of potential markers of T sensitivity is required.

An alternative approach is to evaluate the effects of T administration on women with adverse sexual side effects with OCs. To date only one placebo-controlled study has attempted this (Bancroft et al., 1980). Of 15 women reporting sexual problems with OC use, only one woman showed a clear positive response to exogenous androstenedione (Bancroft et al., 1980).

Are there other possible hormonal mechanisms that might underlie negative effects of OCs on mood or sexuality? Early studies, involving high-dose OCs, compared women using pills varying in the dose of progestagen but the findings were inconsistent; in one study, higher progestagen dosages (Grant and Pryse-Davies, 1968) and in another, lower progestagen formulations (Kutner and Brown, 1972) were associated with depression and loss of libido. In a more recent placebo-controlled study of combined and progestagen-only pills (POP), the POP was associated with no negative effects on sexuality and some improvement in mood (Graham et al., 1995); however, the combined OC, that adversely affected sexuality in a subgroup of women, contained a higher dose of progestagen than the POP.

Our study had several limitations. The small sample size and the single blood sample taken before starting OCs and after 3 months of pill use meant there would have been many sources of random error, increasing the total amount of random variability present in the data. Our sample involved young, predominantly unmarried women; the findings may not be generalizable to other populations of women. There was limited assessment of mood, with only severity of depressive symptoms assessed. Future studies should use broader measures of mood that incorporate positive mood states/well-being.

In conclusion, it appears that a substantial proportion of women who take OCs experience a marked decline in serum androgen levels without adverse sexual effects. What distinguishes women who experience negative sexual side effects from those who do not remains unexplained and a question of crucial importance for future research.

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