

The effects of oral contraceptives on SHBG and free testosterone and their relevance to premenstrual mood and sexual interest: A comparison of two triphasic formulations containing norgestimate and either 35µg or 25µg of ethinyl estradiol.

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Abstract:

Purpose

This study compared two oral contraceptives (OCs) with the same triphasic regimen of progestin (norgestimate 0.18, 0.215 and 0.25 mg) but differing doses of ethinyl estradiol (EE) — 25 and 35 µg EE — in their effects on androgens, mood and sexual interest in women starting on OCs.

Methods

Total testosterone (T), free testosterone (FT), sex-hormone-binding globulin (SHBG) and dehydroepiandrosterone sulphate (DHEA-S), together with measures of mood [Beck Depression Inventory (BDI)], sexual interest [Dyadic and Solitary subscales of the Sexual Desire Inventory (SDI)] and self-reported side effects were assessed before starting on the OC and again after 3 months of use.

Results

Sixty women, all university students, were randomized to receive either the 25 µg EE (N/EE25) or the 35 µg EE (N/EE35) pill; 12 women discontinued, leaving 48 who completed the 3-month study. Their mean age was 19.7 years (18–30) and they were predominantly white and single. Both OCs produced reductions in mean T [N/EE35: from 1.33 to 0.60 nmol/L, $p < .001$; N/EE25: from 1.12 to 1.02 nmol/L; nonsignificant (NS)] and FT (N/EE35: from 41.3 to 4.4 pmol/L,

$p < .001$; N/EE25: from 25.4 to 7.9 pmol/L, $p < .01$), but the reduction in both T and FT was significantly greater with the higher EE dose (N/EE35) ($p = .05$ and $p = .03$, respectively). DHEA-S was also reduced with both formulations (N/EE35: from 7.26 to 5.22 $\mu\text{mol/L}$); N/EE25: from 7.50 to 5.39 $\mu\text{mol/L}$), although the reduction was only significant in the N/EE35 group ($p < .02$). Considerable variability in changes in mood was evident with both OCs, with some women showing predominantly negative effects (10 in N/EE35, 5 in N/EE25); others, positive effects (9 in N/EE35, 17 in N/EE25) and some, no change (four in each group). Women using N/EE25 were significantly more likely to show improvement in premenstrual mood than those in the N/EE35 group ($p < .02$), although there was no correlation between changes in BDI and FT or DHEA-S. Sexual interest scores did not change significantly from baseline to posttreatment with either OC (N/EE35: dyadic, from 40.5 to 39.6, NS; solitary, from 5.9 to 6.4, NS; N/EE25: dyadic, from 36.7 to 37.0, NS; solitary, from 5.0 to 4.2, NS).

Conclusion

The lower EE pill reduced FT less and was associated with greater improvement in premenstrual mood. A causal relation between these two effects is uncertain.

Keywords: androgens | mood | premenstrual | oral contraceptives | sex | contraceptives | sexual behavior | sexual health

Article:

1. Introduction

When oral contraceptives (OCs) were initially marketed, there was concern that they caused depression in some women, particularly those using pills with high doses of ethinyl estradiol [1]. With the introduction of lower dose pills, there has been less concern about depressive illness, but a number of studies have looked at mood changes relevant to quality of life. Overall, the conclusions are that some women experience improved mood with OCs; some, worse mood and the largest proportion, no change [2] and [3]. The literature on the impact of OCs on premenstrual syndrome (PMS) also reports different effects [4]. Some women find their perimenstrual mood changes are worse when using OCs, and this may lead to their early discontinuation [5]. Others may experience improvement in mood, possibly related to an OC-induced reduction in other cycle-related symptoms, such as premenstrual and menstrual pain. Improvement in premenstrual mood symptoms with OC use has been reported recently [6], although studies incorporating a placebo control have not shown significant difference between OC and placebo [7] and [8].

Less attention has been paid to sexual side effects, although systematic studies of women starting on OCs have reported negative effects on sexuality in a proportion of women, but some reported

positive effects, and many, no change [2] and [9]. Explanations for these varied effects have remained elusive, although a number of possibilities have been considered [2] and [3]. Sanders et al. [5], after assessment before starting OCs, found that negative changes in mood and sexuality were the strongest predictors of discontinuation within the first year. Not only does this warrant closer examination of these early effects of OCs, it also reminds us that much of the limited evidence on mood and sexuality in OC users involves women with long-term OC use. Those who have these negative effects are likely to be not included in cross-sectional studies because of early discontinuation.

Although individual characteristics may make some women more vulnerable to negative OC effects, an understanding of what OC-induced mechanisms are involved is clearly important. In particular, is it the estrogen or the progestin that is responsible, or does it depend on interaction between the two? It has been recognized for some time that combined steroidal OCs lower free testosterone (FT), mainly by blocking ovarian production of total testosterone (T) and reducing the percentage of FT (%FT) by stimulating sex-hormone-binding globulin (SHBG) production. Estradiol stimulates SHBG production by the liver, whereas T suppresses it [10]. Different OC formulations vary in the extent to which FT is lowered.

Several studies show a positive relationship between androgen levels and well-being in women, although the clearest relation is with dehydroepiandrosterone (DHEA) [11] or DHEA sulfate (DHEA-S) [12]. Considerable attention is being paid currently to the role of T in women's sexuality, although the evidence is inconsistent overall [13]. It is therefore noteworthy that there has been virtually no research that has directly examined OC-induced reduction in serum androgen levels in relation to changes in women's mood or sexuality.

In this article, we focus on the possible impact of different doses of estrogen on FT and DHEA-S levels and also on self-report measures of mood and sexuality in women starting on OCs. Previous studies that have compared OCs with different EE dosage have either restricted their attention to physical side effects and cycle control or have measured changes in FT, but not both. Two such studies have solely assessed hormonal effects. Coenen et al. [14] compared the effects of four OCs on androgen levels. Two of the OCs contained the same dosage of progestagen (desogestrel 150 μ g) but differing dosages of EE (30 and 20 μ g, respectively). The other two formulations contained 250 μ g norgestimate/35 μ g EE and 75 μ g gestodene/30 μ g EE. All four OCs produced substantial reductions in FT, with no difference between pill groups in this respect. DHEA-S was also significantly reduced in all four pill groups, although less in the 20 μ g EE/150 μ g desogestrel group. Boyd et al. [15] studied a new OC, which used norethindrone acetate (1 mg) combined with a three-phase EE regimen (20 μ g for the first 5 days, 30 μ g the

next 7 days and 35 µg for nine days). Levels of FT decreased progressively as the EE dose increased through the OC cycle. DHEA-S was not measured.

In studying side effects and acceptability, Akerlund et al. [16] used a double-blind randomized design to compare women starting on one of two OCs, both containing 150 µg desogestrel, but with either 20 µg EE or 30 µg EE, and followed them up over 12 months. The only information given in the paper about the assessment of side effects was that “occurrence of side effects was recorded at each follow-up visit.” On this basis, they found significantly more reports of “mood change” with the lower EE formulation than with the higher EE pill (8.6% vs. 4.3%, respectively, $p < .05$). Endrikat et al. [17] compared two OCs with the same progestagen (gestodene 75 µg) and either 20 or 30 µg of EE. Their assessment of adverse changes was based on questioning “using nonleading terms”; presumably, women only indicated what they believed to be side effects or felt comfortable discussing. The most substantial difference between the two OCs was a higher rate of intermenstrual bleeding in the low EE group. Only 3.3% of women using the 30-µg and 1.8% using the 20-µg pill complained of “change in libido,” and 2.1% and 0.9%, respectively, complained of “depressive moods.”

Overall, from this limited literature, when controlling for the progestagen used, lower-EE-dosage OCs appear to be associated with more side effects than higher-EE OCs.

Caruso et al. reported two studies [18] and [19] assessing the effects of OCs on women's sexuality, using a validated measure of women's sexuality, the Personal Experience Questionnaire [20]. In the first study [18], they assessed the effect of a monophasic OC with 15-µg EE and 60-µg gestodene in 48 women. They found a significant decrease in sexual arousal and sexual enjoyment by the third month and of sexual desire and frequency of sexual activity by the ninth month of use. In the second study [19], they assessed an OC with 30 µg of EE and 3 mg of drospirenone, using the same methods of assessment. Here, they found a significant improvement in sexual enjoyment and orgasm frequency from the third month onwards. No hormonal assessments were carried out in either study, and it is not possible to conclude whether these substantial differences in sexual effects were due to the different EE dose or the different progestagen, or a combination of both.

As was clearly demonstrated in an early study [21], side effects of OCs have been more prevalent in those studies where they have been systematically assessed, rather than relying on

women's spontaneous reporting. This is particularly important with adverse changes in mood and sexuality.

In this article, we present a study comparing two widely used OCs with the same triphasic regimen of progestagen (norgestimate 0.18, 0.215 and 0.25 mg) but different levels of EE (25 and 35 µg), hereafter referred to as N/EE35 and N/EE25. Serum levels of total and free T, SHBG and DHEA-S, as well as mood and sexual interest, were measured before starting the OC and after 3 months of OC use, together with reported side effects.

2. Methods

2.1. Participants

Participants were recruited via advertisements posted at an Indiana University Health Center, the local Planned Parenthood Clinic, the campus newspaper and the Kinsey Institute Web site.

Inclusion criteria included being: 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.

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, antineuroleptics 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 or had known contraindications to OC use were excluded from the 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 OCs. The Indiana University Institutional Review Board approved this study, and informed consent was obtained from all participants.

Of the 106 women who were screened for the study by telephone or face-to-face interview with one of the researchers, 23 were ineligible, 23 were eligible but did not agree to participate and 60 were enrolled in the study.

A single-blinded, parallel group design was used, with random assignment to either N/EE25 or N/EE35. 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. Researchers who interviewed the participants were blinded to the study drug, but to allow clinical continuity

of care at the University Health Center, women were given the normal pill packets and instructions, and consequently, they were not blinded. Women were informed that the purpose of the study was only to examine “the effects of birth control pills on androgen levels and sexuality.”

Participants were assessed prior to starting the OC and again after 3 months of OC use. At the first assessment, they were allocated (single blind) to one of the study groups by being provided with 3 months supply of OCs in a numbered sealed opaque envelope.

2.2. Behavioral assessment

After providing informed consent and before starting the OC, study participants were interviewed and asked to complete questionnaires. This assessment was repeated after 3 months of OC use. The following measures are reported in this article:

2.2.1. Beck Depression Inventory

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 combined range of 0–63. Scores from 0–9 are considered to indicate minimal, 10–16 mild, 17–29 moderate and 30–63 severe depression [22]. Due to possible variation of mood through the menstrual cycle, each woman completed the Beck Depression Inventory (BDI) on the first day of her period to cover the premenstrual week and start of menses. It is therefore important to emphasize that it was this phase of the cycle that was assessed.

2.2.2. Sexual Desire Inventory

This validated measure of sexual desire is based on the conceptualization of sexual desire as “interest in sexual activity” [23]. Two aspects of sexual interest are measured: “dyadic desire” is interest in sexual activity with another person, and “solitary desire” is an interest in engaging in sexual behavior by oneself (e.g., masturbation). Ratings are made of sexual interest over the last month. The dyadic and solitary subscale scores have ranges of 0–70 and 0–40, respectively (higher scores indicate higher levels of sexual interest).

The BDI and Sexual Desire Inventory (SDI) were completed at both the initial assessment, referred to in the results as “pre,” and again at the 3-month assessment (“post”).

2.2.3. Side effects questionnaire

This interviewer-administered assessment included a list of 18 side effects presented to the participant [5] and [9]. Both direction of change (positive or negative) and extent of change (none 0, mild 1, moderate 2 and marked 3) 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. [5], three mean summary scores were calculated for positive and negative changes: physical side effects (headaches, feeling bloated, tender breasts, weight gain, nausea, aches and pains, skin changes, abdominal cramps and tiredness); emotional side effects (feeling better in mood, feeling worse in mood, more emotional and less emotional) and sexual side effects (loss of sexual interest, increased sexual interest, loss of sexual enjoyment, increased sexual enjoyment and lack of vaginal lubrication).

2.2.4. Menstrual health questionnaire

This questionnaire was completed at baseline [5], [9] and [24]. This covers various aspects of menstrual, contraceptive and pregnancy history, and includes questions about previous treatment for depression. Only the history of treated depression and self-report of experience of PMS will be reported in this article. Women indicated whether they usually had severe, moderate, mild or no PMS prior to starting the OC.

2.3. Hormonal assessment

Blood samples were taken ± 2 days around ovulation in the last pre-OC cycle (based on their usual cycle length) and in the same window of time during the third cycle of OC use. Each sample was assayed for T, SHBG, %FT, FT and DHEA-S. DHEA-S was the adrenal androgen assayed, as DHEA-S rather than DHEA had been the hormone shown to be lowered by OCs [14] and was also the hormone assessed in the most substantial study of androgens and well-being [12].

Total T was measured with a Spectria Testosterone RIA kit obtained from Orion Diagnostica (Oulunsalo, Finland). Assay performance was validated using calibrated serum standards, based on comparison with RIA preceded by chromatography, 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 [25].

SHBG concentrations were determined using a time-resolved immunoassay kit (PerkinElmer Life and Analytical Sciences, Wellesley, MA, USA). Assay performance was monitored by inclusion of control samples provided by the kit manufacturer, and interassay 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 reanalyzed at a 1:400 dilution to ensure accuracy of measurement. Samples were analyzed in duplicate. If duplicate measurement exceeded 10% of the mean, samples were reanalyzed to ensure accuracy of measurement.

Free T was calculated from a nomogram constructed using serum SHBG concentrations, and the %FT was measured by centrifugal ultrafiltration dialysis [26] 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 data set reported in Ref. [25]). The nomogram allows %FT to be predicted from SHBG values, and this value is then used to determine FT levels from T measurements.

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

2.4. Statistical methods

Data were entered into Excel and transferred to SPSS version 13.0 (SPSS, Chicago, IL, USA) for statistical analysis. Data are presented as n (%) or mean (S.D.), as appropriate. To compare scores between the study groups, chi-squared (χ^2) tests were used for categorical data and Mann–Whitney tests for continuous data. Continuous data were categorized where appropriate. Associations between variables were assessed using Spearman correlation coefficient (rs).

Statistical significance was taken at $p < .05$ throughout, with 95% CIs used to express uncertainty around the estimates.

3. Results

Of the 60 women who were recruited into the study, 12 (20%) (seven on N/EE35 and five on N/EE25) did not complete the study (see Fig. 1 for flow diagram). Four of these women were lost to follow-up (two N/EE35, two N/EE25), and eight women discontinued. The reasons women gave for discontinuing were: lack of time ($n=1$; N/EE35), side effects ($n=4$; 2 N/EE35, 2 N/EE25), relationship ended ($n=1$; N/EE35), became pregnant ($n=1$; N/EE25), wanted to conceive ($n=1$; N/EE35). Only two baseline variables were related to discontinuation: women who discontinued were more likely to report sexual problems [$\chi^2(1)=7.4$, $p=.01$] and were more likely to report that religion was only “slightly” or “not important to them” (vs. “very important” or “important”) [$\chi^2(1)=12.2$, $p=.001$], compared with women who completed the study.

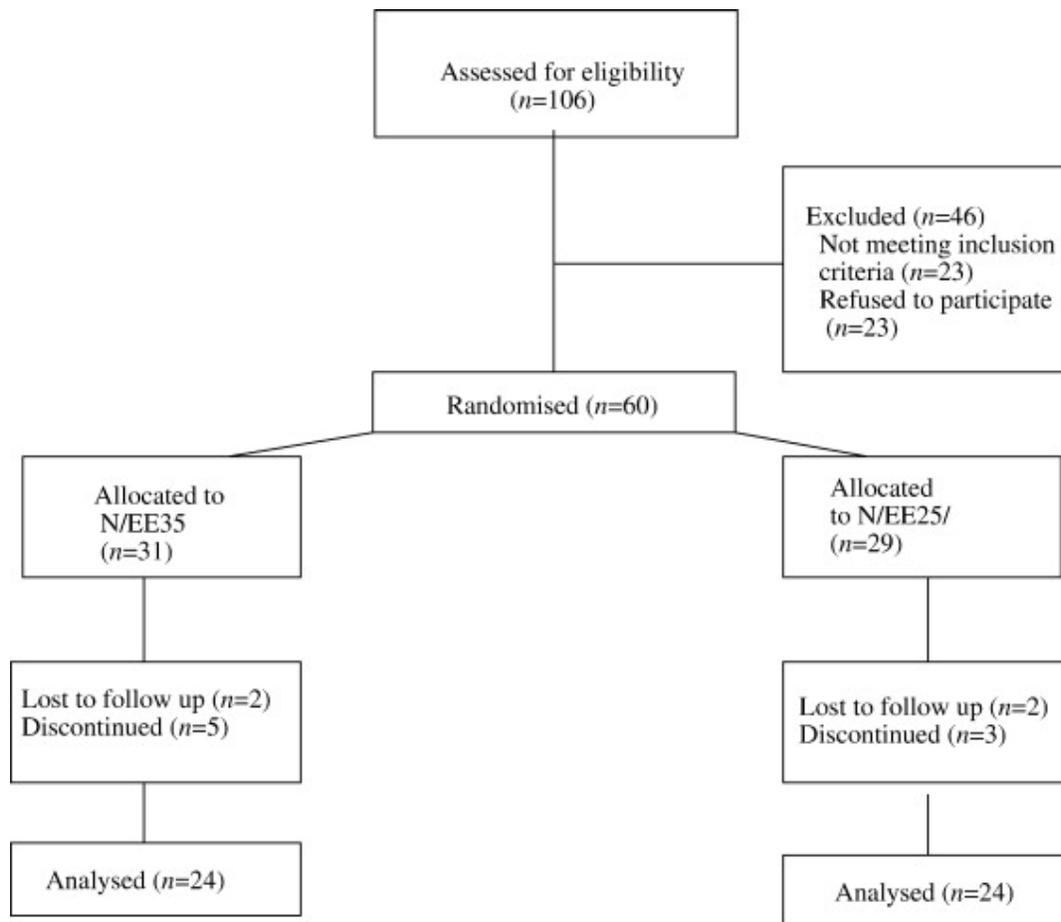


Fig. 1.

Flow diagram of participation.

Of the 48 women who completed the study, 24 had been assigned to the N/EE35 group, and 24, to the N/EE25 group. The mean ages (\pm S.D. and range) for the two groups were 19.7 \pm 2.4 (18–30) and 19.9 \pm 1.3 (18–24) years, respectively. The sample was predominantly white (85%) and single (92%), and all but one of the women was nulliparous. The two groups were well matched for demographic variables, except for duration of their current sexual relationship (see Table 1), which was, on average, twice as long in the N/EE25 group. Because of missing data for some measures, the number of participants is less than 48 for some analyses.

Table 1.

Characteristics for the N/EE35 and N/EE25 groups

Demographic/Background variable	N/EE35 (<i>n</i> =24)	N/EE25 (<i>n</i> =24)
Age (years) [mean (S.D.)]	19.7 (2.2)	19.9 (1.3)
Range	(18–30)	(18–24)
Race		
White	18 (78.3)	22 (91.7)
Asian	2 (8.7)	1 (4.2)
Black or African American	1 (4.3)	1 (4.2)
Other minorities	2 (8.7)	0 (0)
Marital status		
Single/never married	22 (91.7)	22 (91.7)
Living with partner, but not married	1 (4.2)	2 (8.3)
Married	1 (4.2)	0 (0)
Length of relationship (months) [mean (S.D.)]	12.4 (13.0)	24.3 (18.9)
Range	3–48	3–60

Values are given as *n* (%) unless otherwise stated.

3.1. Hormonal measures

The levels of T in nmol/L, %FT, FT in pmol/L, SHBG in nmol/L and DHEA-S in mmol/L for the pretreatment month (pre) and after 3 months on OC (post), together with the change scores for each variable from pre to post, are shown for the two pill groups in Table 2. For the N/EE35 group, the reduction in T was significant ($p < .001$). For FT, the reductions were significant for

both groups ($p < .001$ and $p < .01$, respectively). The reductions in T and FT were significantly greater with N/EE35 than N/EE25 ($p = .05$ and $.03$, respectively). The increases in SHBG, 460.5% for N/EE35 and 386.2% for N/EE25, were not significantly different. DHEA-S was reduced by both pills (N/EE35: from 7.26 to 5.22 $\mu\text{mol/L}$; N/EE25: from 7.50 to 5.39 $\mu\text{mol/L}$), but the difference was only significant with the N/EE35 pill ($p < .02$).

Table 2.

Serum concentrations of T, %FT, FT, SHBG and DHEA-S before starting on OCs (pre), after 3 months of OC use (post) and pre–post change

Serum variable		N/EE35 (n=24)	N/EE25 (n=24)	Mean difference ^a	95% CI (lower, upper)	p ^b
T (nmol/L)	Pre	1.33 (0.87)	1.12 (0.72)	-0.21	-0.27, 0.69	.40
	Post	0.60 (0.44)	1.02 (1.24)	0.41	-0.51, 0.12	.12
	Change	-0.73 (1.0)	-0.10 (1.1)	0.63	-1.24, -0.02	.05
%FT pre	Pre	2.83 (0.89)	2.37 (0.91)	-0.46	-0.07, 0.99	.12
	Post	0.70 (0.18)	0.68 (0.19)	-0.025	-0.08, 0.13	.33
	Change	-2.12 (0.79)	-1.69 (0.86)	0.43	-0.92, 0.05	.09
FT (pmol/L)	Pre	41.3 (38.1)	25.4 (19.0)	-15.90	-1.98, 33.7	.19
	Post	4.4 (3.8)	7.9 (12.9)	3.50	-9.12, 2.00	.28
	Change	-36.9 (38.3)	-17.4 (18.4)	19.50	-0.04, -0.002	.03
SHBG (nmol/L) pre	Pre	46.5 (35.7)	55.9 (26.9)	9.40	-0.28, 9.20	.12
	Post	232.1 (111.4)	252.8 (103.2)	20.70	-83.9, 42.4	.30
	Change	185.6 (97.6)	197.0 (88.2)	11.40	-66.1, 43.4	.35
DHEA-S ($\mu\text{mol/L}$)	Pre	7.26 (3.2)	7.50 (4.4)	-0.24	-2.49, 2.02	.83
	Post	5.22 (2.3)	5.39 (3.8)	-0.17	-2.00, 1.65	.85
	Change	-2.05 (2.26)	-2.11 (2.8)	-0.06	-1.43, 1.55	.94

Values are given as mean (S.D.).

^a N/EE35–N/EE25.

b p Value for MannWhitney *U* test.

3.2. Behavioral measures

3.2.1. Mood

On average, scores on the BDI, our measure of negative mood for the premenstrual week, decreased slightly (i.e., improvement in mood) in both groups after 3 months on the OC, and there was a trend for this improvement to be greater in the N/EE25 group (see Table 3). There was considerable variability, however, in the direction of change. With N/EE35, BDI scores decreased (i.e., improvement in mood) in nine (39%) women and increased (i.e., deterioration in mood) in 10 (43%), with four (17%) women showing no change. With N/EE25, 17 (74%) women showed a decrease; five (22%), an increase and one (4%), no change. Women using the 25- μ g-EE pill were significantly more likely to report a decrease in BDI or improvement in mood than women using the 35- μ g-EE pill [$\chi^2(1)=5.66$, $p<.02$].

Table 3.

Beck Depression Inventory before starting on OCs (pre), after 3 months of OC use (post) and pre-post change

BDI score	N/EE35 (<i>n</i> =23)	N/EE25 (<i>n</i> =23)	Mean difference ^a	95% CI (lower, upper)	<i>p</i> ^b
Pre	8.6 (7.2)	10.4 (7.9)	-1.80	-6.31, 2.66	.43
Post	8.0 (7.8)	7.2 (7.9)	-0.80	-3.73, 5.39	.63
Change	-.61 (7.8)	-2.87 (10.3)	-2.26	-3.17, 7.69	.09

Values are given as mean (S.D.).

a N/EE35–N/EE25.

b p Value for Mann-Whitney *U* test.

There was no correlation between change in BDI score and reduction in FT ($r_s=.027$), or between BDI score post and level of FT Post ($r_s=.012$). There was also no correlation between change in BDI score and reduction in DHEA-S ($r_s=.05$).

The numbers of women in each group who, before starting on OCs described themselves as having PMS, were as follows: moderate or severe PMS was reported by five (23%) in the N/EE35 and six (26%) in the N/EE25 group; mild PMS, by nine (41%) in the N/EE35 and 14 (61%) in the N/EE25 group; no PMS, by eight (36%) in the N/EE35 and three (13%) in the

N/EE25 group. There were thus more women with PMS using N/EE25 (90% vs. 64%), though this was not significant [$\chi^2(2)=3.16$, $p=.21$]. There was an association between the baseline BDI score, which covers the preceding premenstrual week, and self-report of PMS. Combining the two pill groups, mean (S.D.) BDI scores were: no PMS, 3.2 (3.2); mild PMS, 8.5 (6.3) and moderate/severe PMS 15.8 (7.8) [$F(2,42)=10.74$, $p<.001$]. The association between self-report of PMS and change in BDI score for premenstrual mood on the OC, for the two pill groups combined, is shown in Table 4; this showed a trend ($p<.10$), with women reporting no PMS being more likely to show no change in BDI score.

Table 4.

Association between self-reported PMS history and change in BDI scores (pre–post) for total sample ($n=43$)

BDI	No PMS	Mild PMS	Moderate/severe PMS ^a	Total
Mood improved	2 (22.2)	14 (58.3)	5 (41.6)	21 (46.7)
No change	6 (66.6)	4 (16.6)	4 (33.3)	14 (31.1)
Mood worsened	1 (11.1)	6 (25.0)	3 (25.0)	10 (22.2)
Total	9 (100)	24 (100)	12 (100)	45 (100)

Values are given as n (%). $\chi^2(4)=7.83$, $p=.098$.

a Only one woman indicated “severe” PMS symptoms.

Five women reported a previous history of treated depression, two in the N/EE35 and three in the N/EE25 group. The average change in BDI score for these five women was zero (one showed a substantial increase; the other four, a small decrease).

To explore the possible relevance of duration of current relationship, the two pill groups were combined, and women showing improvement in mood ($n=26$) were compared with those showing no change or deterioration in mood ($n=20$). There was a trend for the improved group to have had longer relationships (improved: 22.5 months \pm 19.7; no change/worse: 14.1 months \pm 12.2; $t(44)=1.78$, $p<.10$).

3.2.2. Sexual interest

The SDI dyadic score, a measure of interest in sexual interaction with a partner, was significantly lower in the N/EE25 group at baseline, but the change after 3 months of OC was not significant in either group. The two pill groups were also not significantly different in terms of change in SDI dyadic scores (Table 5). However, as with the BDI, both groups reported varied changes. In the N/EE35 group, the SDI dyadic score decreased in 14 women (58%) and increased in 10 (42%); for the N/EE25 group, scores decreased in 12 (50%) and increased in 12 (50%) [$\chi^2(1)=.00$, $p=1.00$].

Table 5.

Sexual Desire Inventory scores before starting on OCs (pre), after 3 months of OC use (post) and pre–post change

SDI subscale	N/EE35 (n=24)	N/EE25(n=24)	Mean difference ^a	95% CI (lower, upper)	p ^b
Dyadic					
Pre	40.5 (6.4)	36.7 (7.1)	−3.80	−0.12, 7.70	.04
Post	39.6 (7.9)	37.0 (10.0)	−2.60	−2.58, 7.91	.36
Change ^c	−.83 (5.5)	0.29 (7.8)	1.12	−5.04, 2.79	.53
Solitary					
Pre	5.9 (4.8)	5.0 (4.9)	−0.90	−1.98, 3.65	.53
Post	6.4 (5.2)	4.2 (3.9)	−2.20	−0.48, 4.90	.12
Change ^c	0.5 (3.3)	−0.9 (2.4)	−1.40	−0.32, 3.07	.40

Values are given as mean (S.D.).

a N/EE35 minus N/EE25.

b p Value for Mann-Whitney *U* test.

c Pre–post change was NS.

The SDI solitary score, a measure of interest in individual sexual activity such as masturbation, did not change significantly with either pill. With N/EE35, nine (38%) decreased, eight (33%) increased and seven (29%) showed no change. With N/EE25, the numbers were nine (38%), five (21%) and 10 (42%), respectively [$\chi^2(1)$ improvement vs. other=.00, $p=1.00$].

3.2.3. Relation between sexual interest and mood

There were no significant correlations between SDI scores and BDI at baseline (SDI dyadic vs. BDI, $r_s=.048$, $p=.75$; SDI solitary vs. BDI $r_s=.197$, $p=.19$).

3.3. Side effects

The numbers of women reporting predominantly negative or positive physical, emotional and sexual side effects are shown in Table 6. More positive physical side effects were reported with N/EE35, and more positive emotional side effects with N/EE25, although the differences were not significant. There was a trend for more women using N/EE25 to report intermenstrual bleeding ($p=.096$).

Table 6.

Number (%) of women reporting worsening (–), improvement (+) or no change (0), of physical, emotional and sexual side effects and prevalence of intermenstrual bleeding for two pill groups ($n=48$)

Pill group	Physical			Emotional			Sexual			Intermenstrual bleeding	
	–	+	0	–	+	0	–	+	0	Yes	No
N/EE35 ($n=24$)	11 (45.8)	12 (50.0)	1 (4.2)	11 (45.8)	5 (20.8)	8 (33.3)	8 (33.3)	9 (37.5)	7 (29.2)	3 (12.5)	21 (87.5)
N/EE25 ($n=24$)	14 (58.3)	6 (25.0)	4 (16.7)	9 (37.5)	9 (37.5)	6 (25.0)	8 (33.3)	5 (20.8)	11 (45.8)	9 (37.5)	15 (62.5)
	$\chi^2(2)=4.16$, $p=.123$			$\chi^2(2)=1.26$, $p=.533$			$\chi^2(2)=2.03$, $p=.362$			$\chi^2(1)=2.8$, $p=.096$	

Eighteen women from the two groups combined reported improvement in perimenstrual pain on OCs. Of these, 12 also showed improvement in mood. However, five women reported worsening of pain, and of these, four showed improvement in mood; there was no significant association between change in pain and change in mood [$\chi^2(4)=5.99$, $p=.20$].

4. Discussion

This study involved comparison of two OCs with different dosages of EE but the same triphasic dose of progestagen (norgestimate) randomly assigned to two groups of women. These two groups were well matched with the exception that, by chance, women taking the lower-dose OC (N/EE25) were in relationships of longer duration. The possible implications of this will be considered below. All the women were, however, students with an average age of nearly 20 years, predominantly white and single. We cannot therefore assume that results reported here would also be found in older married women.

4.1. Hormonal changes

There has been increasing attention in recent years to the methodological problems in measuring serum testosterone in women, with concerns about the reliability of direct RIA in the lower part of the physiological range [27]. In a recent large scale, community-based study of androgens, sexuality and well-being in women [28], a direct RIA was used. This had been validated by comparison with RIA following solvent extraction and column chromatography in a subsample of the women [29]. Testosterone measured by the direct RIA was around 60–70% of the levels obtained with RIA following chromatography. However, the difference was fairly consistent across the range and was encouragingly good in the lower part of the range. In our study, we also used a direct RIA, which had been validated by comparison with RIA plus chromatography. The method used for estimating FT from T has also been a matter of concern. Equilibrium dialysis has been recommended as a “gold standard” by some [27]. The method used in our study is based on centrifugal ultrafiltration dialysis [26], which we consider to be even better, not suffering from problems with equilibrium dialysis such as sample dilution and tracer instability during the prolonged incubations, which contribute to an overestimation of free hormone levels. We nevertheless acknowledge difficulties in measuring T levels in women, and our results should be treated with caution. With that caveat, we will consider our principal hormonal findings.

Both OCs resulted in reductions of T and FT, although these were significantly greater with the higher-EE-dose OC. Average reduction in T was seven times greater with the high-EE pill (N/EE35), and reduction in FT more than double that of the low-EE pill (N/EE25). There was also a substantial increase in SHBG; although this was greater with the high-EE pill, the difference was not significant. Given the reduction in total T as well as FT, this raises the possibility that direct suppression of T formation by the higher EE dose contributed to the different patterns. Both OCs reduced DHEA-S, although the reduction was only significant with the N/EE35 pill. These findings are partially consistent with previous studies [14] and [15]. They are similar in terms of OC-induced androgen reduction, but they are not similar in terms of differential effects of the EE dosage of the OC. Coenen et al. [14] found that high- and low-EE

dosages produced similar reduction in T and FT, both in the third and sixth OC cycle. The low-EE dose produced significantly less reduction of DHEA, but this differential dosage effect was only evident after six OC cycles, not after three. Boyd et al. [15], investigating an OC with triphasic EE dosage, found the T levels decreased proportional to the EE dose, in the third cycle. Various factors may contribute to the inconsistencies across these studies, including different progestagens, different time periods on OC and, of course, potential variance due to the assays.

4.2. Changes in mood

There was considerable variability in the change scores for the BDI with only five women overall showing no change. This is consistent with previous evidence of effects of OCs on mood, as discussed in the introduction. Oinonen and Mazmanian [3], in their review of the literature, concluded that the most common pattern was an improvement in mood with OC use, which they attributed to greater mood stability and less negative mood during menstruation. In the present study, we can only comment on mood during the premenstrual week, and this raises the issue of PMS. Only one woman described herself as having severe PMS, with 12 reporting moderate and 23 mild PMS. The clear association between these ratings and BDI scores for the premenstrual week at baseline provides some validation for these self-assessments. We cannot, however, make clear diagnoses of PMS or premenstrual dysphoric disorder (PMDD) according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria [30], and it is unlikely that more than one or two women would have met those stringent criteria, particularly in this young age group. It is possible, however, that the mild or moderate patterns of premenstrual symptoms, reported by 75% of the women in this study, are relevant to acceptability of OCs, particularly if there is improvement or worsening in these symptoms. We found only a trend in the association between PMS history and either improvement or worsening of premenstrual mood on the OC. However, it may be unhelpful to consider PMS and/or PMDD as unitary phenomena.

An alternative model was proposed by Bancroft [4], who suggested that three factors interact to result in the variable cyclical patterns typically referred to as PMS or PMDD. A “timing factor” involves the normal cyclical variation in a number of potentially relevant hormones, including estradiol, progesterone and androgens. It was postulated that this pattern results in variability in brain mechanisms influencing mood, which for the majority of women is not problematic and, for many, may not even be noticeable. The “menstruation factor” points to the impact of menstruation, which can either be positive, as shown by a striking relief of premenstrual symptoms with onset of bleeding in some women, or negative, resulting in enhanced premenstrual and menstrual negative mood, related in some way to pain and/or heavy bleeding. The third “vulnerability” factor refers to noncyclical characteristics of the individual that render her vulnerable to the negative effects of either of the other two factors. Steroidal contraceptives

are relevant to each of these three factors. Monophasic OCs counteract, whereas, to some extent, triphasic OCs reinforce the “timing factor.” This is shown by evidence that women on monophasic OCs experience more stable mood during the pill cycle than women taking phasic OCs, though with an increased likelihood of mood change during the pill withdrawal phase [31]. Most types of OC may counteract the negative aspects of the “menstruation factor” in those women in whom menstrual pain or heaviness of bleeding is reduced. OCs may also aggravate the “vulnerability factor”; in a comparison of triphasic and monophasic OCs, women with a tendency to premenstrual mood change showed more negative mood on the triphasic pill, usually occurring during mid cycle [32].

Using the above model of perimenstrual change, the impact of OCs on menstrual cycle-related symptoms is likely to be variable, depending in part on characteristics of the woman and in part on the type of OC. Unfortunately, we do not have a sample large enough to identify these different types of interaction with any certainty, though there are some indications. Women using the lower EE pill were significantly more likely to show improvement in mood. They were also more likely to report PMS, particularly mild PMS, and there was a nonsignificant trend towards PMS reporters showing more improvement in mood. Seven women taking N/EE35 and 12 women taking N/EE25 reported reduction in menstrual pain. There was also a trend towards mood improvement being more likely in women experiencing reduction of pain. The few women with a previous history of depression did not show more mood change on OCs.

The difference in duration of the sexual relationship in the two pill groups is of possible relevance. The trend showing longer duration in those women reporting improvement in mood could partially account for the greater improvement in mood with the N/EE25 group. How this would be mediated is not clear but needs to be explored in future studies.

4.3. Changes in sexual interest

The two groups had significantly different SDI dyadic scores at baseline, which may have been related to the longer duration of relationship in the N/EE25 group. As with mood, changes in our measures of sexual interest after starting OCs were variable in both groups. However, we found no significant differences between the two OCs in this respect. In the N/EE35 group, the mean baseline and posttreatment SDI dyadic scores were 40.5 and 39.6; SDI solitary scores were 5.9 and 6.4. In the N/EE25 group, baseline and posttreatment SDI dyadic scores were 36.7 and 37.0; SDI solitary scores were 5.0 and 4.2. None of these changes from baseline were significant (see Table 5). There was also no consistent relationship between mood change and change in sexual interest. Although in some individuals changes in sexual interest may be secondary to mood

change, other mechanisms also need to be considered. As shown in a placebo-controlled evaluation of an OC as a treatment for PMS [7], improvement in mood can be accompanied by a decline in sexual interest.

The possibility that the low EE OC might be associated with more problems of vaginal dryness was only weakly supported; nine women in the N/EE25 group reported this as a side effect compared with seven in the N/EE35 group.

4.4. The relevance of hormonal changes to mood and sexuality

What role may the OC-induced hormonal changes play in these subtle differences between the pill groups? Recent evidence suggests that androgens have a positive impact on mood and well-being [11], [12] and [33]. As both pill groups in the present study experienced reduction in T, there is no obvious direct explanation for the observed differences in improvement in mood. However, the lesser reduction of T with N/EE25 might allow other nonhormonal factors to produce positive mood effects, for example, by reducing concerns about unwanted pregnancy; this could be relevant to the duration of the relationship. DHEA has a clearer association with well-being than T [12]. If we had found less reduction in DHEA-S with our low-EE-dose OC, as had been shown previously [14], this would have been consistent with a less negative effect of N/EE25 on mood.

Previous studies, as reviewed earlier, have found a higher side effects profile in lower EE OCs [16] and [17]. Our findings are consistent with this, which makes the greater tendency for mood improvement in the low EE group all the more interesting.

The literature on androgens and sexuality in women is inconsistent. Androgens appear to have an enhancing effect on women's sexuality but not in all studies or all women. To account for this interindividual variability, it has been postulated that women vary in their behavioral sensitivity to T [13]. As yet, however, markers of such sensitivity, other than response to T change, have not been identified. These results would suggest 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. This issue is addressed in more detail in a separate article where participants in this study are combined with others to form a larger sample [34].

This is the first study that we are aware of that has systematically evaluated both behavioral and hormonal changes in women starting on OCs, but it involves small samples, and some of our trends may have occurred by chance. The choice of OCs was based on their both being widely used, while having contrasting EE doses and the same progestagen, norgestimate. However, there are a number of active metabolites of norgestimate, which could have been produced in different amounts among our participants, adding to the variance in the data. Further studies with larger samples are clearly necessary, both using the same OCs and also comparing other OCs with different progestagens. Larger sample size should also facilitate identification of other nonhormonal factors of relevance to OC effects, such as premenstrual mood change.

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References

- C.R. Kay. The Royal College of General Practitioners' Oral Contraception Study: some recent observations. *Clin Obstet Gynecol*, 11 (1984), pp. 759–786
- J. Bancroft, N. Sartorius. The effects of oral contraceptives on well-being and sexuality. *Oxf Rev Reprod Biol*, 12 (1990), pp. 57–92
- K.A. Oinonen, D. Mazmanian. To what extent do oral contraceptives influence mood and affect? *J Affect Disord*, 70 (2002), pp. 229–240
- J. Bancroft. The premenstrual syndrome — a reappraisal of the concept and the evidence. *Psychol Med Monogr*, 24 (Suppl) (1993), pp. 1–47
- S.A. Sanders, A. Borsos, C.A. Graham, J. Bass, J. Bancroft. A prospective study of the effects of oral contraceptives on sexuality and well-being and their relationship to discontinuation. *Contraception*, 64 (2001), pp. 51–58
- D. Apter, A. Borsos, W. Baumgartner et al. Effect of an oral contraceptive containing drospirenone and ethinylestradiol on general well-being and fluid-related symptoms. *Eur J Contracept Reprod Health Care*, 8 (2003), pp. 37–51

C.A. Graham, B. Sherwin. The relationship between mood and sexuality in women using an oral contraceptive as a treatment for premenstrual symptoms. *Psychoneuroendocrinology*, 18 (1993), pp. 273–281

E.W. Freeman, R. Kroik, A. Rapkin et al. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *J Womens Health Gen Based Med*, 10 (2001), pp. 561–570

C.A. Graham, R. Ramos, J. Bancroft, C. Maglaya, T.M.M. Farley. The effects of steroidal contraceptives on the well-being and sexuality of women: a double-blind, placebo-controlled, two-center study of combined and progestogen-only methods. D.C. Anderson. Sex-hormone-binding globulin. *Clin Endocrinol*, 3 (1974), pp. 69–96

E.H.H. Cawood, J. Bancroft. Steroid hormones, the menopause, sexuality and well-being of women. *Psychol Med*, 26 (1996), pp. 925–936

R.J. Bell, S. Donath, S.L. Davison, S.R. Davis. Endogenous androgen levels and wellbeing: differences between pre- and postmenopausal women. *Menopause*, 13 (2005), pp. 65–71

J. Bancroft. The endocrinology of sexual arousal. Starling review. *J Endocrinol*, 186 (2005), pp. 411–427

C.M.H. Coenen, C.M.G. Thomas, G.F. Borm, J.M.G. Hollanders, R. Rolland. Changes in androgens during treatment with four low-dose contraceptives. *Contraception*, 53 (1996), pp. 171–176

R.A. Boyd, E.A. Zegarac, E.L. Posvar, M.R. Flack. Minimal androgenic activity of a new oral contraceptive containing norethindrone acetate and graduated doses of ethinyl estradiol. *Contraception*, 63 (2001), pp. 71–76

M. Akerlund, A. Rode, J. Westergaard, Comparative profiles of reliability, cycle control and side effects of two oral contraceptive formulations containing 150µg desogestrel and either 30µg or 20µg ethinyl oestradiol, *Br J Obstet Gynaecol*, 100 (1993), pp. 832–838

J. Endrikat, U. Muller, B. Dusterberg, A twelve-month comparative clinical investigation of two low-dose oral contraceptives containing 20µg ethinylestradiol/75µg gestodene, and 30µg ethinylestradiol/75µg gestodene, with respect to efficacy, cycle control, and tolerance. *Contraception*, 55 (1997), pp. 131–137

S. Caruso, C. Agnello, G. Intelisano, M. Farina, L. Di Mari, A. Cianci. Sexual behavior of women taking low-dose oral contraceptive containing 15µg ethinylestradiol/60µg gestodene. *Contraception*, 69 (2004), pp. 237–240

- S. Caruso, C. Agnello, G. Intelisano et al. A prospective study on sexual behavior of women using 30µg ethinylestradiol and 3 mg drospirenone oral contraceptive. *Contraception*, 72 (2005), pp. 19–23
- L. Dennerstein, E.C. Dudley, J.L. Hopper, H. Burger. Sexuality, hormones and the menopausal transition. *Maturitas*, 26 (1997), pp. 83–93
- P.P. Talwar, G.S. Berger. A prospective, randomized study of oral contraceptives: the effect of study design on reported rates of symptoms. *Contraception*, 20 (1979), pp. 329–337
- A.T. Beck, R.A. Steer. Beck Depression Inventory (BDI). American Psychiatric Association (Ed.), *Handbook of psychiatric measures*, American Psychiatric Association, Washington (DC) (2000), pp. 519–523
- I.P. Spector, M.P. Carey, L. Steinberg. The Sexual Desire Inventory: development, factor structure and evidence of reliability. *J Sex Marital Ther*, 22 (1996), pp. 175–190
- J. Bancroft, L. Williamson, P. Warner, D. Rennie, S. Smith. Perimenstrual complaints in women complaining of PMS, menorrhagia and dysmenorrhoea; towards a dismantling of the “premenstrual syndrome”. *Psychosom Med*, 55 (1993), pp. 133–145
- G.L. Hammond, L.S. Abrams, G.W. Creasy, J. Natarajan, J.G. Allen, P.K. Siiteri. Serum distribution of the major metabolites of norgestimate in relation to its pharmacological properties. *Contraception*, 67 (2003), pp. 93–99
- G.L. Hammond, J.A. Nisker, L.A. Jones, P.K. Siiteri. Estimation of the percentage of free steroid in undiluted serum by centrifugal ultrafiltration-dialysis. *J Biol Chem*, 255 (1980), pp. 5023–5026
- G. Bachmann, J. Bancroft, G. Braunstein et al. Female androgen deficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertil Steril*, 77 (2002), pp. 660–665
- S.R. Davis, S.L. Davison, S. Donath, R.J. Bell. Circulating androgen levels and self-reported sexual function in women. *JAMA*, 294 (2005), pp. 91–96
- S.L. Davison, R. Bell, J.G. Montalto et al. Measurement of total testosterone in women: comparison of a direct radioimmunoassay versus radioimmunoassay after organic solvent extraction and celite column partition chromatography. *Fertil Steril*, 84 (2005), pp. 1698–1704
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., Text Rev), American Psychiatric Association, Washington (DC) (2000), pp. 771–774
- A. Walker, J. Bancroft. The relationship between premenstrual symptoms and oral contraceptive use: a controlled study. *Psychosom Med*, 52 (1990), pp. 86–96

J. Bancroft, D. Sanders, P. Warner, N. Loudon. The effects of oral contraceptives on mood and sexuality: a comparison of triphasic and combined preparations. *J Psychosom Obstet Gynaecol*, 7 (1997), pp. 1–8

P.J. Schmidt, R.C. Daly, M. Bloch et al. Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. *Arch Gen Psychiatry*, 62 (2005), pp. 154–162

C.A. Graham, J. Bancroft, H.A. Doll, T. Greco, A. Tanner. Does oral contraceptive-induced reduction in free testosterone adversely affect the sexuality and mood of women? *Psychoneuroendocrinology*, 32 (2007), pp. 246–255