Psychoneuroendocrinology 76 (2017) 135–143

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Combined oral contraceptive use is associated with both improvement and worsening of mood in the different phases of the treatment cycle—A double-blind, placebo-controlled randomized trial

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ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form
28 November 2016
Accepted 28 November 2016

Keywords:
Randomized clinical trial
Combined oral contraceptives
Estrogen
Progestagen
Depression
Anxiety
Irritability

ABSTRACT

Objective: Ever since the introduction of combined oral contraception (COC), one of the major reasons for discontinuing the pill use has been mood-related side effects. Moreover, women who discontinue the pill turn to less effective methods whereby the probability of an unintended conception increases. Approximately 4–10% of COC users complain of depressed mood, irritability or increased anxiety, but drug-related causality has been difficult to prove. Given the lack of randomized controlled trials in this area, we aimed to prospectively estimate the severity of adverse mood in COC users that would be as representative of general users as possible.

Methods: This investigator-initiated, multi-center, randomized, double-blinded, placebo-controlled study included 202 healthy women. Women were randomized to a COC (1.5 mg estradiol and 2.5 mg nomegestrolacetate) or placebo for three treatment cycles. Main outcome measure was the Daily Record of Severity of Problems (DRSP), which was filled out daily during one baseline cycle and the final treatment cycle.

Results: Results from 84 women in the COC group and 94 women in the placebo group were analysed. COC use was associated with small, but statistically significant, increases in mean anxiety (0.22; 95% CI: 0.07–0.37, p = 0.003), irritability (0.23; 95% CI: 0.07–0.38, p = 0.012), and mood swings scores (0.15; 95% CI: 0.00–0.31, p = 0.047) during the intermenstrual phase, but a significant premenstrual improvement in depression (−0.33; 95% CI: −0.62 to −0.05, p = 0.049). Secondary analyses showed that women with previous adverse hormonal contraceptive experience reported significantly greater mood worsening in the intermenstrual phase in comparison with healthy women, p < 0.05. The proportion of women who reported a clinically relevant mood deterioration did not differ between those allocated to COC (24.1%) or placebo (17.0%), p = 0.262.

Conclusion: COC use is associated with small but statistically significant mood side effects in the intermenstrual phase. These findings are driven by a subgroup of women who clearly suffer from COC-related side effects. However, positive mood effects are noted in the premenstrual phase and the proportion of women with clinically relevant mood worsening did not differ between treatment groups.

1. Introduction

While cross-sectional epidemiologic studies most commonly report that combined oral contraceptive (COC) users are less

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http://dx.doi.org/10.1016/j.psyneuen.2016.11.033
0306-4530/

afflicted by depression and anxiety in comparison with non-users, an increasing number of reports suggest that hormonal contraception (HC)-induced mood symptoms is a reality for some women (Poromaa and Segebladh, 2012). In the Scandinavian countries, mental side effect is the major reason for discontinuing COC use (Lindh et al., 2009), and in doing so, women turn to less effective contraceptive alternatives, thus increasing their risk of unplanned pregnancies (Segebladh et al., 2009). Approximately 4–10% of COC users complain of depressed mood, irritability or increased anxiety, but drug-related causality has been difficult to prove (Poromaa and Segebladh, 2012). Previous studies have emphasized that women with preexisting mood disorders are more inclined to discontinue contraceptive use than healthy women. For instance, we have previously shown that more than 30% of women who discontinue oral contraceptive use because of mood symptoms fulfill criteria for depressive and/or anxiety disorders (Segebladh et al., 2009), and longitudinal studies have suggested that drop-outs more often suffer from depressed mood at baseline than women who continue oral contraceptive use (Joffe et al., 2003).

Previous placebo-controlled COC trials in healthy women have not been able to demonstrate any differences in depressed mood between users of COC and placebo, presumably because the majority of COC users remain unaffected (Graham et al., 1995; Leeton et al., 1978; O'Connell et al., 2007). Yet another alternative explanation to the absence of findings is that none of these studies were representative for the young women who need contraception today. Two of the studies only included sterilized women or women whose partner was sterilized, and the third study included women with dysmenorrhea with very high baseline levels of depression. We have previously reported on a randomized controlled trial (RCT), where women with past complaints of emotional side effects from COC use were randomized to a levonorgestrel-containing pill or placebo (Gingnell et al., 2013). A significant worsening of depressed mood and mood swings was noted, but only one third of these susceptible women experienced a clear-cut mood worsening during COC use (Gingnell et al., 2013). However, it is yet unknown what consequences COC use has in terms of mental health for the general population of users.

To further complicate the matter, it should be emphasized that COC use may also positive effects on mood in certain subgroups. For instance, a low-dose drospirenone-containing pill was shown to have beneficial effect for treatment of premenstrual dysphoric disorder (PMDD) (Lopez et al., 2012), ultimately suggesting that mood influence by hormonal contraception may vary in-between women, and uniform responses across the treatment cycle should not be expected.

Given the large number of women world-wide who are using hormonal contraception, the amount of research exploring what consequences these compounds may have for their mental health and wellbeing is strikingly low. Hence, this investigator-initiated, double-blinded, placebo-controlled trial study aimed at prospectively estimating the severity and prevalence of adverse mood in a population of women that would be as unselected as possible.

2. Material and methods

2.1. Participants

This investigator-initiated study was carried out at the Departments of Obstetrics and Gynecology at Uppsala University Hospital, the Karolinska University Hospital, Södersjukhuset, Linköping University Hospital, Örebro University Hospital, Umeå University Hospital, and Närhälsan Maternity Health Care Center in Frölunda, Gothenburg, between September 7, 2013 and September 29, 2015. Healthy women (18–35 years) with a body mass index below 30 kg/m^2 who accepted to use back-up contraception during the study period were recruited by advertisement in local newspapers, local boards and studentsíwebsites.

The intent was to sample a study population that would be as representative of general users as possible, and for that reason no study-specific exclusion criteria were employed. Instead, the standard exclusion criteria for COC prescription, used in the clinic, were applied; these included family history of venous thromboembolism, more than one risk factor for venous thromboembolism, known thrombophilia, systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, known dyslipidemia, migraine with focal symptoms, inflammatory disorders, first degree relatives with cardiovascular disease at a young age, previous cancer, liver diseases, previous pancreatitis, and use of treatments that would compromise uptake or metabolism of the contraceptive.

However, ongoing psychiatric disorders and present use of psychotropic drugs such as serotonin reuptake inhibitors and benzodiazepines were not reason for exclusion. Also, women who reported previous adverse mood symptoms while using COC were allowed to participate, but records on all of these potential confounders were carefully kept. Women were asked about previous contraceptive use, and prior experiences of COCs using a standardized interview.

Presence of ongoing primary depressive and anxiety disorders was established by use of the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Women were categorized as suffering from any mood disorder if they fulfilled criteria for major or minor depressive disorder or dysthymia. Similarly, women who fulfilled diagnostic criteria for panic disorder, generalized anxiety disorder, social phobia, and obsessive-compulsive disorder were classified as any anxiety disorder. Probable premenstrual syndrome (PMS), according to ICD-10 criteria, and probable PMDD according to DSM-5, was established by daily prospective symptom ratings on the Daily Record of Severity of Problems (DRSP) during one month prior to randomization. Probable PMS was defined as >50% increase in at least two of eleven symptoms between the follicular (day 6–12) and luteal phase (day −7 to −1), whereas probable PMDD was defined as >50% increase in at least five of eleven symptoms (among which at least one symptom was a core PMDD symptom) between the follicular and luteal phase (see Eisenlohr-Moul et al., 2016 for comparisons among various PMDD diagnostic methods). Percent increase was calculated as (mean luteal phase scores − mean follicular phase scores/mean follicular phase scores) × 100. As the definitions of PMS and PMDD require symptom ratings during at least two months, our one-month baseline data merely serve as an indication of PMS or PMDD diagnoses among participants.

The women were fully informed about the study aims and procedures and gave written informed consent prior to inclusion. Upon completion, the participants were reimbursed. The study procedures were in accordance with ethical standards for human experimentation, and the study was approved by the Regional Ethical Review Board, Uppsala and the Medical Products Agency in Sweden. The clinical trial identifier is: EUDRA-CT 2013-000925-30.

2.2. Study design

The study was an investigator-initiated, double-blinded, randomized, parallel-group clinical trial during which the participants were treated with either a COC (1.5 mg estradiol and 2.5 mg nomegestrolacetate) or placebo during three 24/4 treatment cycles. We chose a pill that would have minimal impact on mood, based on the 24/4 dosing schedule, the content of a highly progesterone-selective progestagen, and prior comparisons with a drospirenone-containing pill (Witjes et al., 2015; Pearlstein et al., 2005; Yonkers et al., 2005).

Following a screening visit, women kept daily symptom diaries for one menstrual cycle (baseline cycle), during which no hormonal contraceptive use was allowed. After the baseline cycle was completed, women started taking the COC or placebo tablets once daily on the first day of menses and continued treatment for 24 days, followed by four pill-free days, repeated in three treatment cycles. After two treatment cycles, the participants met with the study nurse in order to receive treatment for the third and final cycle. The last visit was made during the final week of active treatment. Any adverse events or change in concomitant medication were actively asked for and registrered at each visit.

Apoteksbolaget Production and Laboratories (APL, the National Corporation of Swedish Pharmacies) in Stockholm prepared identical capsules containing either COC or placebo. The packing and randomization was done by APL, Stockholm, Sweden. The randomization was determined by a computerized random-number generator in blocks of four and allocation was implemented by use of numbered containers. Upon randomization, the participants were distributed the numbered container with the lowest available number. During the study, the participants and study personnel were not informed about which treatment the patient received and randomization codes were held at the Uppsala University Hospital Pharmacy until completion of the study. Upon completion of the study, participants brought back empty containers, together with the DRSP ratings. Remaining capsules were counted by the study nurses.

The primary outcome measure was the change scores (Δ-scores) in the daily, prospective symptom ratings of all mood and physical symptoms on the DRSP scale (Endicott et al., 2006) across three menstrual cycle phases (intermenstrual, premenstrual and menstrual). Secondary outcomes included change in Montgomery-Åsberg Depression Rating Scale (MADRS-S), change in DRSP Δ-scores in relation to background characteristics such as previous experience of adverse mood on COCs, probable PMS or PMDD, or ongoing mood disorder. Finally, based on the DRSP ratings, secondary outcomes also included treatment response (across all cycle phases) and clinically relevant mood deterioration, as defined below.

The DRSP is typically used to establish a diagnosis of premenstrual dysphoric disorder (PMDD), and monitor treatment response in women with PMDD. The choice of this instrument as primary outcome measure was based on our previous experience in this field, suggesting that COC-induced mood symptoms in many aspects resemble those typically reported by women with PMDD (Borgstrom et al., 2008; Gingnell et al., 2013). The DRSP consists of 21 items that reflect the 11 candidate symptoms for PMDD; depression, anxiety, mood swings, irritability, decreased interest in usual activities, difficulties concentrating, fatigue, sleep disturbances, appetite, sense of being overwhelmed and physical symptoms. Each item is scored on a 6-point Likert scale, with 6 representing maximum severity, and 1 representing a complete absence of a particular symptom. For the purpose of this study, we report on the mean scores for depression, mood swings and irritability, which are captured by several items on the DRSP scale. Women filled out the DRSP during the baseline cycle and the final treatment cycle. To ensure that the pill-free interval and the menstrual phase would be captured completely during the final treatment cycle, women were asked to continue daily symptom ratings one week after last tablet intake. Notably, women also kept records of menstrual bleeding throughout the entire study on a separate bleeding chart, by which menstrual cycle phase was possible to determine.

At the screening visit and the final treatment visit, women filled out the self-rated version of the Montgomery-Åsberg Depression Rating Scale (MADRS-S) (Montgomery and Asberg, 1979). The MADRS-S scores reflect depressive symptoms during the past three days on a scale ranging from 0 to 54. Although the MADRS-S is primarily designed to detect change, a score of 15 or more is commonly used in Swedish primary care to screen for ongoing depression, and was considered as sub-clinical depression in this study. A MADRS-S score >20 was used as a suggestion of a clinically relevant depression.

2.3. Statistical analyses

Power analysis for the primary outcome measure was based on Gingnell et al. (2013), assuming Δ-score differences of 0.6 DRSP scale steps between COC and placebo users, and standard deviations between 0.9–1.7 depending of group allocation. Given a sample size of 100 women in each group, and an expected drop-out of 20%, the study had 80% power to detect a difference between treatments. Notably, the study was not powered to detect a difference in the proportion of women who developed a clinically relevant mood deterioration, which was one of the secondary aims. According to our pre-study estimates (10% in the active treatment group and 5% in the placebo group), for such an aim we would have needed a sample size of at least 540 women in each treatment arm.

2.3.1. Primary outcomes

Results were analysed according to intention-to-treat, and primary analyses were performed with unblinded data. Demographic data were compared between groups by Student's *t*-tests or Chi-square tests. As the COC used in this study is associated with a 30% occurrence of absent withdrawal bleeding (Mansour et al., 2011), we calculated mean daily symptoms scores for the menstrual phase (mean scores of day 1–4 from onset of menses), the premenstrual phase (mean scores of day −1 to −7 prior to menses) and intermenstrual phase (mean score of the remaining cycle days) for each DRSP symptom, to ensure that baseline and treatment cycles would be comparable both within, and between individuals. The DRSP scores of women who developed amenorrhea contributed to the intermenstrual phase. DRSP Δ-scores were calculated as difference between the mean scores of the intermenstrual, premenstrual and menstrual phases, respectively, between the final treatment cycle and the baseline cycle. Statistical analyses were made by linear mixed models ANOVA using the DRSP Δ-scores. Participants were entered as subjects, with menstrual phase as repeated variable, and first order autoregressive repeated covariance type. Menstrual phase and treatment were entered as fixed factors, and the maximum likelihood estimation method was used. An interaction term between treatment and menstrual phase was included as a fixed factor to assess the treatment response in each of the menstrual phases. In case of significant main effects of treatment or treatment by cycle phase interactions, post hoc tests were performed by Mann-Whitney *U* tests.

2.3.2. Secondary outcomes

MADRS-S scores were compared between groups by Mann-Whitney *U* tests or Chi-square tests.

Change in DRSP in relation to background characteristics such as previous experience of adverse mood on COC, probable PMS or PMDD, or present mood disorder (with or without ongoing treatment) was evaluated. Women who suffered from none of the above conditions were denoted healthy controls (n = 98). In these analyses we used the percent change in the summed scores of anxiety, irritability, mood swings and decreased interest in usual activities for each cycle phase. The percent change was calculated as: (mean summed scores of the final treatment cycle − mean summed scores of the baseline cycle/mean summed scores of the baseline cycle) × 100. The percent change were compared between groups by use of two-way linear mixed models ANOVA with menstrual phase as repeated variable and group as fixed factor. An interaction term between cycle phase and group was included as fixed factor.

For analyses on treatment response mean scores of anxiety, irritability, mood swings and decreased interest in usual activities for the entire baseline and final treatment cycle were calculated, i.e. all 28 days. These scores were summed and the percentage change was calculated as above. *Clinically relevant* mood worsening was defined as greater than 30% increase in summed mean scores of anxiety, irritability, mood swings and decreased interest in usual activities during the final treatment cycle *and* a DRSP score ≥2 during the final treatment cycle for at least two of these symptoms. Chi-square tests were used to compare the treatment response, and the clinically relevant mood worsening between the COC and placebo.

The SPSS statistical package was used for the analyses (IBM, Armonk, NY, US). P-values of less than 0.05 were considered to be statistically significant.

2.4. Results

2.4.1. Subjects

More than 700 women expressed an interest in participating in the study. Of these, 224 women were screened and 202 women were randomized, Fig. 1. One hundred-two women were randomized to the COC and 100 women to placebo. Of these, 18 women allocated to the COC intervention and 6 women allocated to the placebo arm dropped out at various stages of the study, resulting in an overall drop-out rate of 11.9%. The most common reason for drop-out was withdrawal of consent, but five women in the COC group discontinued because of side effects, and one woman in the placebo group became pregnant. Finally, 84 women in the COC group and 94 women in the placebo group completed the trial, and complete DRSP scores from the baseline and final treatment cycles were available in 80 women randomized to COC and in 88 women on placebo.

Women randomized to COC or placebo did not differ in terms of age, parity, educational level, history of COC use, previous reports of COC-induced mood symptoms, depression or anxiety or prevalence of probable PMS or PMDD, Table 1. Compliance was excellent; none of the women had more than 1–2 remaining capsules at the end of the study. Fifty-seven (67.9%) women randomized to COC and 59 (63.4%) women randomized to placebo correctly guessed their treatment at the end of the study, p = 0.6. Sixteen (19.0%) women in the COC group and eight (8.5%) women in the placebo group had amenorrhea during the final treatment cycle, p = 0.054. Adverse events are presented in Supplementary Table 1. Thirty-four (33.3%) women randomized to COC spontaneously reported mood side effects, whereas corresponding number among women randomized to placebo was 21 (21.0%), p = 0.049. No serious adverse events were reported.

The median baseline DRSP scores across the intermenstrual, premenstrual and menstrual phases are shown in Table 2. While no differences in mood scores were noted during the baseline cycle, women later randomized to COC tended to have higher scores of depression and decreased interest in usual activities.

2.4.2. Primary outcome

2.4.2.1. Differences in DRSP Δ-scores between placebo and active treatment. Significant treatment by menstrual cycle phase interactions were noted for irritability Δ-scores (F[2,286]; 3.00: p = 0.019) and anxiety Δ-scores (F[2,266]; 3.19: p = 0.043), Table 3. In addition, trends toward treatment by menstrual phase interactions were also noted for Δ-scores of depression, and sense of being overwhelmed, Table 3. Furthermore, a borderline significant main effect of treatment was noted for mood swings Δ-scores, Table 3. All of these findings were further explored by use of post hoc Mann-Whitney *U* tests. According to the post hoc tests, significant worsening in the intermenstrual phase was noted among oral contraceptive users in anxiety (mean difference 0.22; 95% CI: 0.07–0.37, p = 0.003), irritability (mean difference 0.23 95% CI: 0.07–0.38, p = 0.012) and mood swings (mean difference 0.15 95% CI: 0.00–0.31, p = 0.047). Notably, COC use was associated with a significant premenstrual improvement in depression (mean difference −0.33 95% CI: −0.62 to −0.05, p = 0.049). No other significant findings were noted in the post hoc analyses.

The differences in the intermenstrual phase were further analysed, by dividing the intermenstrual phase into relevant menstrual cycle phases, Fig. 2. Women randomized to combined oral contraceptives displayed higher summed Δ-scores of anxiety, mood swings, and irritability, and decreased interest in usual activities during cycle days 8–14 and 15–21, but not on days 5–7, of the final treatment cycle in comparison with women randomized to placebo. The greatest numerical differences in summed raw mood scores between treatments were noted during days 6–9 of the final cycle, Supplementary Fig. 1.

2.4.3. Secondary outcomes

2.4.3.1. Depression scores. No difference in MADRS scores were found at baseline or during treatment, Tables 2 and 3. Similarly, the proportion of women with depression scores in the clinical (≥20) or subclinical (≥15) ranges did not differ during treatment (MADRS ≥ 20, COC; 4(4.8%) vs. placebo; 1(1.1%), p = 0.132, MADRS ≥ 15, COC; 11(13.3%) vs. placebo; 7(7.4%), p = 0.202). Finally, the number of women with new-onset subclinical depression during treatment did not differ between the oral contraceptive group and the placebo group, (COC; 8(9.6%) vs. placebo; 6(6.4%), p = 0.423).

2.4.3.2. Symptom ratings in relation to baseline characteristics. Change in summed scores of anxiety, mood swings, and irritability, and decreased interest in usual activities across menstrual cycle phases and treatment allocation, and according to the relevant baseline characteristic are displayed in Fig. 3. Women with previous adverse hormonal contraceptive experience reported significantly greater mood worsening in the intermenstrual phase in comparison with healthy women during active treatment, p < 0.05. No other differences according to baseline characteristics were noted.

2.4.3.3. Treatment response and clinically relevant mood worsening. The overall proportion of women with improved or worsened mood during the entire treatment cycle is displayed in Fig. 4. Improved as well as worsened summed mood scores were found during the treatment cycle, however, placebo users more often reported mood improvement and COC users more often reported mood worsening, linear-by-linear association, p = 0.045. Nineteen (24.1%) COC users reported a clinically significant mood worsening in comparison with 15 (17.0%) placebo users, p = 0.262.

3. Discussion

The results of this randomized controlled trial suggest that use of a COC containing 1.5 mg estradiol and 2.5 mg nomegestrolacetate is associated with small but significant mood side effects in the intermenstrual phase. However, the study also demonstrates that positive effects can be expected in the premenstrual phase, and some women show overall improvement of mood.

The study demonstrated that the adverse mood symptoms most responsive to hormonal contraceptive exposure are anxiety, irritability and mood swings. The mood changes in this trial were minimal, typically at the group level less than half a scale-step, and were driven by women who reported previous adverse experience with COC use. While these differences may appear small, they are explained by the fact that many women also improved throughout the trial. However, for some women the mood deterioration was greater than 30 percent, which in line with previous literature

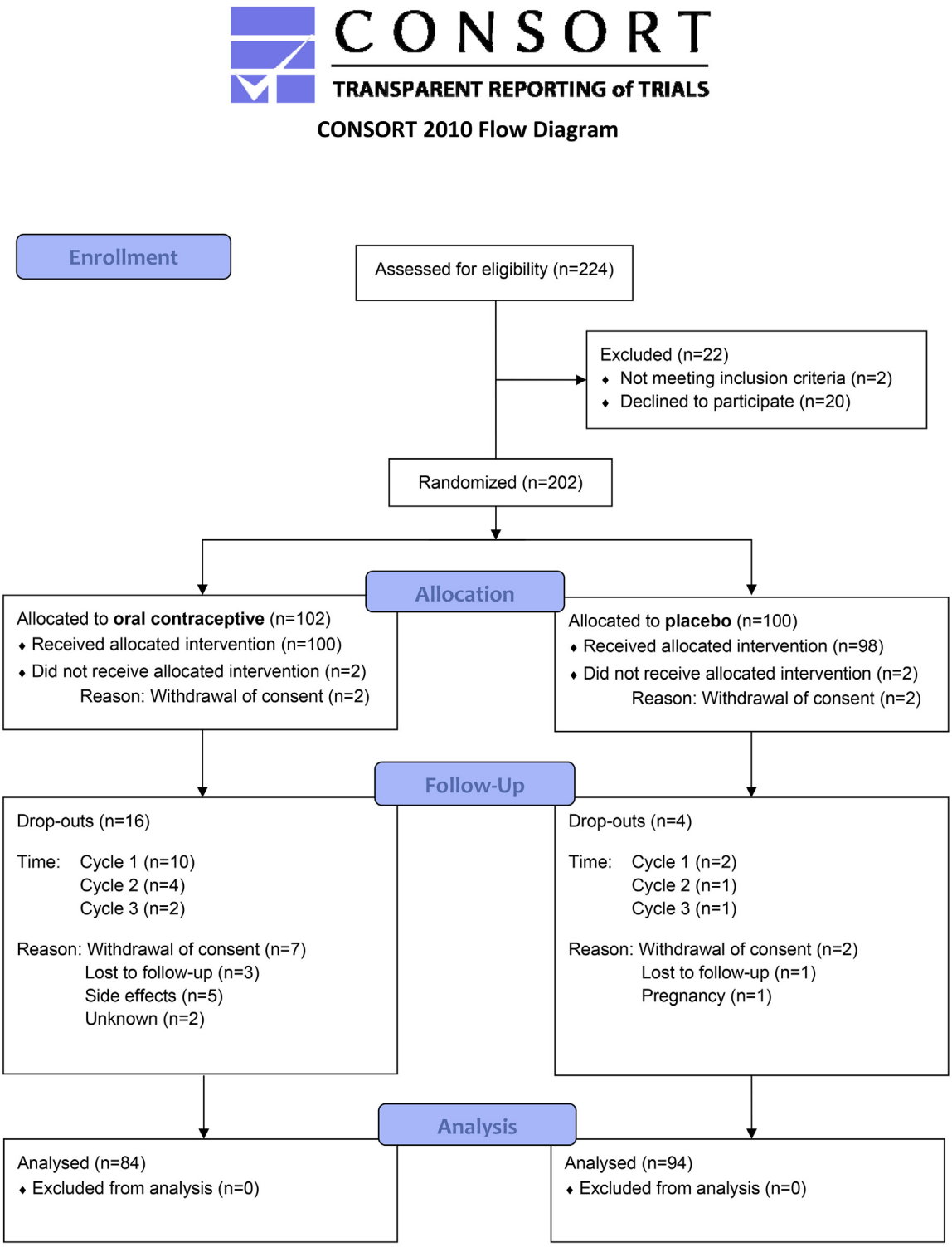

Fig. 1. Flowchart of the study population.

(Poromaa and Segebladh, 2012), underscores the clinical relevance of adverse mood reporting by the COC users. Further, the greater number of drop-outs in the COC treatment arm may have diminished the differences between treatments, as some clearly dropped out due to adverse effects.

Notably, the COC chosen for this study has not specifically been associated with mood worsening previously. In contrast, it seems superior to a drospirenone-containing pill, at least for menstrual phase reports of negative affect, concentration and behavioral changes (Witjes et al., 2015). However, it remains to be determined if the effects seen in this study is a class effect of all progestagens used in contraception or due to this specific compound. Further, head-to-head comparisons are needed to evaluate what contraceptives would be most beneficial for women.

One important finding was that the negative mood effects were only noted in the intermenstrual phase. In previous studies, most emphasis has been placed on demonstrating positive effects in the premenstrual and menstrual phases, where most women experi-

Table 1
Demographic and clinical variables in the study population n = 202. Results are presented as mean ± SD, n (%).

	Combined oral contraceptive n = 102	Placebo n = 100	*p*
Age, years	23.8 ± 4.2	24.8 ± 4.2	0.097
Nulliparous, n%	95 (93.1)	90 (90.0)	0.442
University education, n%	78 (76.5)	75 (76.5)	0.992
BMI, kg/m^2	22.3 ± 2.6	22.5 ± 2.5	0.532
Smokers, n%	7 (6.9)	8 (8.2)	0.737
Previous hormonal contraceptive use, n%	84 (82.4)	82 (82.0)	0.947
Duration of previous hormonal contraceptive use, years	4.8 ± 3.5	4.8 ± 3.3	0.945
Previous adverse mood experience from hormonal contraceptive use, n%	41 (40.2)	38 (38.0)	0.759
Current hormonal contraceptive use			0.288
Never user	18 (17.6)	18 (18.0)	
Starter	70 (68.6)	75 (75.0)	
Switcher	14 (13.7)	7 (7.0)	
Premenstrual syndrome, n%	20 (19.6)	14 (14.6)	0.349
Premenstrual dysphoric disorder, n%	9 (8.8)	6 (6.2)	0.494
Any depressive disorder, n%	9 (8.8)	5 (5.0)	0.285
Any anxiety disorder, n%	7 (6.9)	8 (8.0)	0.785
Current use of psychotropic drugs			0.605
Serotonin reuptake inhibitors	8 (7.8)	5 (5.0)	
Other	2 (2.0)	2 (2.0)	

Frequencies are reported in relation to available responses, missing cases evident in 2–4 cases depending on variable. IQR = interquartile range.

Table 2
Baseline DRSP scores across the intermenstrual, premenstrual and menstrual phases, and according to allocated treatment. Data are presented as median interquartile range.

	Combined oral contraceptive n = 96			Placebo n = 96			*p*	*p*
	Intermenstrual n = 96 median (IQR)	Premenstrual n = 86 median (IQR)	Menstrual n = 84 median (IQR)	Intermenstrual n = 96 median (IQR)	Premenstrual n = 84 median (IQR)	Menstrual n = 82 median (IQR)	Main effect allocation	Allocation × phase interaction
Depression	1.47 (1.17–2.00)	1.57 (1.14–2.14)	1.42 (1.00–2.59)	1.29 (1.11–1.76)	1.43 (1.00–2.00)	1.50 (1.16–2.00)	0.084	0.797
Anxiety	1.43 (1.12–1.82)	1.43 (1.14–2.00)	1.50 (1.00–2.25)	1.41 (1.12–1.88)	1.43 (1.00–1.89)	1.25 (1.00–2.13)	0.336	0.842
Mood swings	1.38 (1.12–2.00)	1.43 (1.13–2.23)	1.75 (1.00–2.50)	1.29 (1.06–1.64)	1.57 (1.14–2.19)	1.50 (1.13–0.25)	0.490	0.117
Irritability	1.35 (1.12–1.73)	1.43 (1.14–2.04)	1.50 (1.00–2.50)	1.29 (1.06–1.55)	1.50 (1.00–2.13)	1.50 (1.00–2.00)	0.298	0.579
Decreased interest in usual activities	1.48 (1.13–1.94)	1.46 (1.05–2.20)	1.50 (1.00–2.50)	1.42 (1.07–1.76)	1.43 (1.14–1.86)	1.50 (1.00–2.00)	0.082	0.329
Difficulties concentrating	1.53 (1.18–2.00)	1.57 (1.14–2.14)	1.50 (1.00–2.50)	1.47 (1.18–2.04)	1.54 (1.14–2.14)	1.50 (1.00–2.13)	0.619	0.849
Fatigue	1.86 (1.41–2.53)	2.00 (1.50–2.57)	2.00 (1.30–2.75)	1.73 (1.35–2.35)	1.86 (1.43–2.50)	2.00 (1.25–2.50)	0.443	0.706
Appetite changes	1.24 (1.06–1.82)	1.43 (1.00–2.16)	1.25 (1.00–2.25)	1.19 (1.05–1.56)	1.43 (1.03–2.11)	1.50 (1.09–2.25)	0.827	0.187
Sleep disturbances	1.76 (1.25–2.42)	1.71 (1.14–2.60)	1.88 (1.00–2.75)	1.67 (1.18–2.24)	1.57 (1.14–2.19)	1.75 (1.00–2.75)	0.380	0.762
Overwhelmed	1.29 (1.06–2.00)	1.29 (1.00–2.16)	1.25 (1.00–2.19)	1.34 (1.00–1.79)	1.15 (1.00–2.00)	1.08 (1.00–1.81)	0.280	0.655
Physical symptoms	1.23 (1.06–1.47)	1.71 (1.14–2.43)	1.75 (1.00–2.97)	1.18 (1.00–1.53)	1.57 (1.12–2.09)	1.75 (1.09–2.75)	0.946	0.766
MADRS-S scores	5 (3–8)			4 (2–8)			0.362	

Statistical comparisons of DRSP scores by mixed model ANOVA, using of log-transformed scores.

Table 3
DRSP Δ-scores across the intermenstrual, premenstrual and menstrual phases during the final treatment cycle. Data are presented as mean ± standard deviation. Negative number indicates improvement; positive number indicates worsening.

	COC n = 80			Placebo n = 88			*p*	*p*
	Intermenstrual n = 80 mean ± SD	Premenstrual n = 44 mean ± SD	Menstrual n = 51 mean ± SD	Intermenstrual n = 88 mean ± SD	Premenstrual n = 65 mean ± SD	Menstrual n = 67 mean ± SD	Main effect treatment	Treatment × phase interaction
Depression	0.11 ± 0.57	−0.13 ± 0.75	−0.02 ± 0.98	0.06 ± 0.61	0.20 ± 0.73	−0.06 ± 0.72	0.393	0.056
Anxiety	0.18 ± 0.54	−0.05 ± 0.78	−0.05 ± 1.12	−0.04 ± 0.46	0.11 ± 0.72	0.03 ± 0.73	0.928	0.043
Mood swings	0.23 ± 0.53	0.13 ± 0.78	0.08 ± 1.20	0.08 ± 0.48	−0.02 ± 1.01	−0.10 ± 0.88	0.086	0.972
Irritability	0.30 ± 0.57	0.03 ± 0.86	−0.09 ± 0.95	0.07 ± 0.46	0.10 ± 0.76	−0.02 ± 0.73	0.262	0.019
Decreased interest in usual activities	0.18 ± 0.65	0.04 ± 1.15	0.02 ± 1.15	0.02 ± 0.51	0.22 ± 0.62	0.06 ± 0.85	0.916	0.224
Difficulties concentrating	0.06 ± 0.60	−0.09 ± 0.76	0.05 ± 0.79	−0.07 ± 0.63	−0.03 ± 0.75	−0.01 ± 0.81	0.581	0.477
Fatigue	0.24 ± 0.64	0.11 ± 1.05	0.16 ± 1.13	0.03 ± 0.74	0.20 ± 0.95	0.18 ± 1.04	0.654	0.413
Appetite changes	0.12 ± 0.62	−0.07 ± 0.64	−0.12 ± 0.89	0.05 ± 0.44	−0.03 ± 0.89	0.04 ± 0.94	0.792	0.459
Sleep disturbances	0.07 ± 0.68	0.06 ± 1.14	−0.16 ± 1.31	0.02 ± 0.77	0.03 ± 1.02	0.01 ± 1.04	0.888	0.631
Overwhelmed	0.14 ± 0.66	−0.14 ± 0.95	0.09 ± 1.10	0.00 ± 0.66	0.18 ± 0.80	0.26 ± 0.85	0.426	0.083
Physical symptoms	0.16 ± 0.75	0.00 ± 0.93	−0.12 ± 1.06	0.01 ± 0.53	0.01 ± 0.91	−0.12 ± 0.83	0.628	0.607
MADRS-S scores, median (IQR)	7 (5–11)			6 (3–10)			0.078	

IQR = interquartile range. For statistical comparisons mixed model ANOVA or Mann-Whitney *U* test was used.

ence problems such as dysmenorrhea, PMS, and PMDD and might expect a symptom relief with the hormonal contraceptive. Indeed, in line with previous studies demonstrating limited beneficial premenstrual effects of 24/4 COC dosing regimens (Lopez et al., 2012;

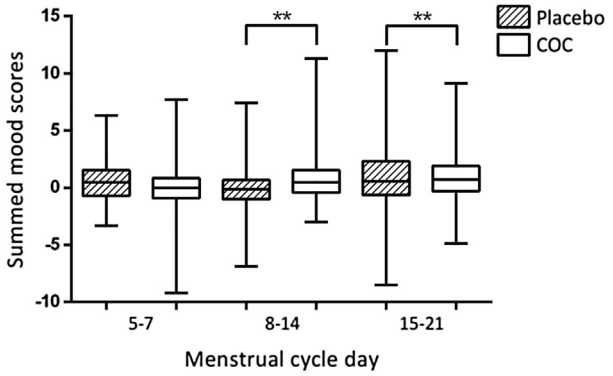

Fig. 2. Box plots of summed Δ-scores of anxiety, irritability, mood swings and decreased interest in usual activities across the intermenstrual phase in oral contraceptive and placebo users. Women randomized to combined oral contraceptives displayed higher mood scores during menstrual cycle days 8–14 and 15–21, but not during cycle days 5–7.
*p < 0.01, Mann-Whitney *U* test.

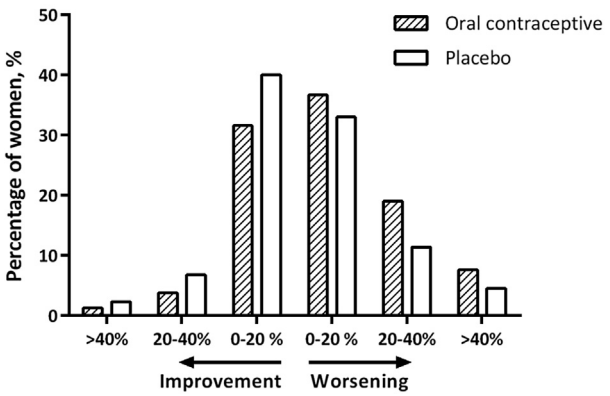

Fig. 4. Proportion of women with improved or worsened summed mood score (anxiety, mood swings, irritability, and decreased interest in usual activities) during the final treatment cycle. A significant linear-by-linear association was noted, p = 0.045.

Pearlstein et al., 2005; Yonkers et al., 2005), we also noted a significant improvement in premenstrual depression. However, the intermenstrual phase has been relatively unexplored previously, and this seem to be the phase of importance for women who complain of COC-induced mood symptoms. The intermenstrual phase, as defined in this study, spanned from day 5 of the menstrual cycle to day 21, but the greatest numerical differences were noted during cycle days 6–9, i.e. when placebo users would have been in their late follicular phase. During this phase, the placebo users would be exposed only to estrogen, and their estrogen levels would be gradually increasing in order to reach preovulatory levels. From an endocrine perspective the findings may thus be due to lower endogenous estradiol levels in the oral contraceptive users, or to the continuous exposure to progestagens throughout the entire COC cycle. Many studies have suggested that estradiol is associated with mood improvement, both during the follicular phase and when used by postmenopausal women (Soares, 2013). In women on 24/4 oral contraceptive regimens, the estradiol suppression seems even greater than in compounds with 21/7 dosing regimens (Sullivan et al., 1999). These findings also fit with the progesterone-induced emotion processing disturbances noted in the luteal phase of the menstrual cycle (Sundstrom Poromaa and Gingnell, 2014) and in oral contraceptive users. For instance, oral contraceptive use has been associated with disturbances in emotional memory (Kuhlmann and Wolf, 2005; Nielsen et al., 2011, 2013), manifested as differential recall of positively and negatively valenced images (Nielsen et al., 2013), or differential recall of central information and the peripheral details from an emotional story (Nielsen et al., 2011). Emotion discrimination, i.e. the ability to recognize facial expressions of emotions, in oral contraceptive users is associated with decreased insula and prefrontal cortex reactivity (Gingnell et al., 2013), decreased amygdala reactivity (Petersen and Cahill, 2015), but increased reactivity in the fusiform face area (Mareckova et al., 2014). Furthermore, oral contraceptive use has also been reported to impair fear extinction (Graham and Milad, 2013). Cross-sectional studies of COC users have indicated that they have increased cortisol levels (Maes et al., 1992; Ansseau et al., 1993), reduced cortisol responsivity (Kirschbaum et al., 1995; Bouma et al., 2009) and lower levels of neurosteroids (Paoletti et al., 2004; Rapkin et al., 2006). Peripheral markers of the serotonin system also appear to be altered in COC users (Weizman et al., 1988; Maes et al., 1992), although no difference in cortical $5HT_{2A}$ binding between COC users and non-users has been demonstrated (Frokjaer et al., 2009). Finally, we have previously reported that women who experience adverse mood while on COC have deficient prepulse inhibition, a measure of sensorimotor gating with relevance for many anxiety disorders (Braff et al., 2001), in comparison with COC users who reported unchanged emotional well-being (Borgstrom et al., 2008).

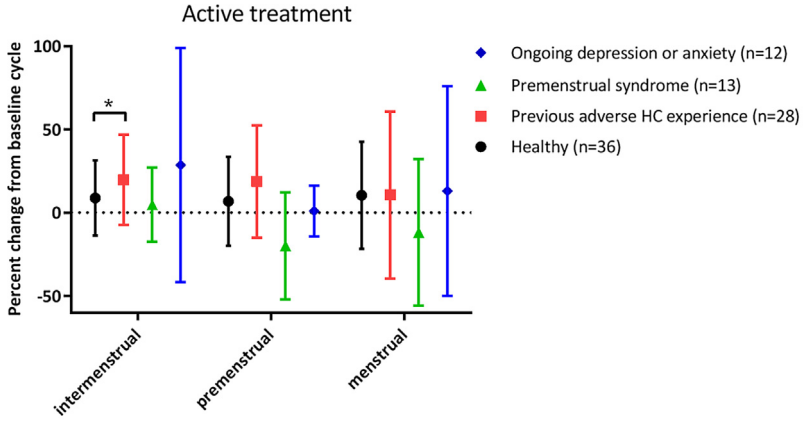

Fig. 3. Percent change in mean summed scores of anxiety, mood swings, irritability and decreased interest in usual activities, across menstrual cycle phases and treatment allocation, and according to relevant baseline characteristic. For clarity reasons are standard deviations not displayed. Women with previous adverse hormonal contraceptive experience reported significantly greater mood worsening in the intermenstrual phase in comparison with healthy women, p < 0.05. No other differences according to baseline characteristics were noted. HC = hormonal contraception. * p < 0.05.

The findings of the present study were primarily driven by a subgroup of women who had a history suggestive of previous COC-induced mood symptoms. While the study strived to include women that would be as reflective as possible of the general user population, it is conceivable that the study has attracted a greater proportion of women who previously had negative experiences of COC. Almost 40% of women who participated in this trial reported that they previously had experienced mental side effects from COC, and these women also reported significantly more pronounced change from baseline than women who were denoted healthy (i.e. women with no previous reports of COC-induced mood worsening, probable PMS or PMDD or ongoing depression or anxiety disorder). This finding may have repercussions for contraceptive counselling. If women claim previous negative influence on their mental health from hormonal contraception, it may be more feasible to suggest long-acting reversible contraception with minimal hormonal impact such as the levonorgestrel intrauterine system or copper intrauterine devices.

Very few women developed a clinically relevant depression during the trial. All in all, four women in the oral contraceptive group and one woman in the placebo group had depression scores that would be suggestive of a major depression upon completion of the trial. This finding is in line with previous studies suggesting no association between COC use and severe psychiatric morbidity (Vessey et al., 1985), although a more recent study suggested that hormonal contraceptive use is associated with an increased risk for depression and anti-depressant treatment (Skovlund et al., 2016). Indeed, for individual women even minor mood changes are noticeable, evidenced by the increasing proportion of women who discontinue oral contraceptive use due to mental side effects (Lindh et al., 2009).

Finally, on the individual level, the proportion of women with clinically relevant mood worsening did not differ between treatment groups. The placebo response was substantial, and many women also improved throughout the trial. However, the study was not powered to detect a statistically significant difference in the proportion of women who deteriorate on active treatment in comparison with placebo, merely to provide some estimate of how common this is. By using the suggested threshold for symptom worsening, and the results of our findings, future studies would need to include at least 530 women in each treatment arm to prove a statistical difference. However, such a trial may not be relevant as many women are unaffected by hormonal contraceptive use.

In conclusion, COC use is associated with small but significant mood side effects, particularly in the intermenstrual phase of the treatment cycle. These findings are driven by a subgroup of women who clearly suffer from COC-induced side effects. However, the proportion of women with prospectively documented mood worsening did not differ between treatment groups.

Conflicts of interest

I Sundstrom-Poromaa serve occasionally on advisory boards or act as invited speaker at scientific meetings for MSD, Bayer Health Care, and Lundbeck A/S. K Gemzell-Danielsson serves on an ad-hoc basis as invited speaker and on advisory boards for MSD/Merck, Bayer AG, Gedeon Richter, HRA-Pharma and Actavis.

Contributors

Authors ISP, KGD, MB were involved in the conception and design of the study. All authors participated in the acquisition of data. ISP and CL did the data analyses, and authors KGD, MB, LM, JB, IL contributed to the interpretation. ISP and CL drafted the article, and all authors revised the manuscript critically for important intellectual content. All authors have approved the final version of the manuscript.

Role of funding source

The Swedish Research Council project K2013-99X-22269-01-3 supported this study. No support was obtained from any pharmaceutical company.

Acknowledgement

The Swedish Research Council project K2013-99X-22269-01-3 supported this study. No support was obtained from any pharmaceutical company.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.11.033.

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