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Prevalence of psychiatric disorders and premenstrual dysphoric symptoms in patients with experience of adverse mood during treatment with combined oral contraceptives

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Abstract

Background: Negative mood symptoms remain one of the major reasons for discontinuation of combined oral contraceptive pills (COCs). The primary aim of this study was to compare the prevalence of mood and anxiety disorders in women with different experience of COCs.
Study Design: Thirty women currently on COCs with no report of adverse mood symptoms, 28 women currently on COCs and experiencing mood-related side effects, 33 women who had discontinued COC use due to adverse mood effects and 27 women who had discontinued COC use for reasons other than adverse mood symptoms were included. Ongoing psychiatric disorders were evaluated by a structured psychiatric interview and prevalence rates of premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) were assessed by daily prospective ratings on the Cyclicity Diagnoser scale.
Results: Women with ongoing or past experience of COC-induced adverse mood, more often suffered from mood disorders than women with no reports of adverse mood while on COC. The prevalence of prospectively defined PMS or PMDD did not differ between prior users with positive or negative experience. Women who had discontinued COC use due to adverse mood symptoms more often had had a legal abortion in the past.
Conclusion: Women with ongoing or past self-reported adverse mood effects from COCs had a significantly increased prevalence of mood disorders.

Keywords: Combined oral contraceptive pills; Estrogen; Progestogen; Depression; Anxiety; Premenstrual syndrome; Premenstrual dysphoric disorder

1. Introduction

The combined oral contraceptive pill (COC) is the most commonly used contraceptive method among young women. Although the majority of women report unchanged or improved mood while on COCs [1], mood-related side effects, such as irritability, mood swings and depressive symptoms, have always been one of the major reasons for discontinuing treatment [2–4].

When studied prospectively, 7% of women on COCs reported increased anxiety and 10% reported increased depressive mood [5] and discontinuation rates due to adverse mood symptoms were 14–21%, depending on age [6].

It can be assumed that not all adverse mood symptoms experienced by COC users are drug-related. Psychiatric history, personality traits, interpersonal relationships and socioeconomic factors are also likely to contribute to adverse events often attributed to COC treatment [2]. It has also been suggested that patients with premenstrual symptoms (PMS) are more likely to suffer from adverse mood symptoms during COC use [7] and that certain combinations or progestogens are less suitable for women with PMS such as triphasic compounds [8] and levonorgestrel-containing COCs [9].

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The purpose of the present study was to evaluate the prevalence of depression and anxiety disorders in current users of COC with and without adverse mood symptoms. However, by also including two groups of prior users, with and without a history of COC-induced adverse mood, we could also prospectively evaluate the prevalence of PMS and premenstrual dysphoric disorder (PMDD) in women who had discontinued COC.

2. Material and methods

2.1. Subjects

This study is part of a larger study evaluating different aspects of adverse mood symptoms in COC users [10]. In brief, 118 women with different experience of COCs were included in the study. Of these, 30 women were currently on COCs with no report of adverse mood symptoms (COC-fine), 28 women were currently on COCs and did experience mood-related side effects (COC-mood), 27 women had discontinued COC use for reasons other than adverse mood symptoms (pCOC-fine) and 33 women had discontinued COC use due to adverse mood effects (pCOC-mood).

Inclusion criteria for COC-fine subjects were that they did not report any adverse mood effects on their current COC and that they had never switched brands due to adverse mood effects in the past. Both pCOC groups had regular menstrual cycles and reported no use of hormonal contraceptives during the last three months. In all groups, patients were excluded if they were on current treatment with any psychotropic drugs.

The women gave written informed consent prior to inclusion in the study. The study was approved by the Independent Research Ethics Committee at Uppsala University.

2.2. Psychiatric disorders

The presence of psychiatric disorders was evaluated using a structured psychiatric interview, the Swedish version of The Mini-International Neuropsychiatric Interview (MINI). The MINI is designed as a brief structured interview across the major Axis I psychiatric disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) *Revised Third Edition*; *DSM, Fourth Edition* (*DSM-IV*) and the *International Statistical Classification of Diseases, 10th Revision*. and is based on a standardized algorithm of questioning [11]. The MINI evaluates a number of mood disorders (major depressive disorder, dysthymia, bipolar disorder) and anxiety disorders (panic disorder, generalized anxiety disorder, obsessive–compulsive disorder, and social phobia). We also assessed two subthreshold diagnoses — minor depressive disorder and anxiety UNS — by use of the MINI.

Ongoing anxiety symptoms were evaluated by the State and Trait Anxiety Inventory [12].

Provisional diagnosis of PMS and PMDD were based on prospective symptom ratings on the Cyclicity Diagnoser (CD) scale [13]. Diagnoses were provisional as they were based on prospective daily ratings made by the women during 36 days after the visit to the clinic and not for two entire menstrual cycles as stipulated in the criteria for PMDD, defined in the *DSM-IV* (1994) or PMS, defined according to the American College of Obstetricians and Gynecologists [14].

Prospective diagnoses of PMS and PMDD were only established in prior users of COC. The CD scale used for this purpose consists of nine negative mood parameters (depression, decreased interest in usual activities, fatigue, irritability, tension, mood swings, lability, difficulties in concentrating and sleeping disturbances), two positive mood parameters (cheerfulness and energy), and four somatic symptoms (food cravings, swelling, breast tenderness and menstrual bleeding). The CD scale is a Likert scale ranging from 0 to 8, with 0 as complete absence of a particular symptom, and 8 as the maximal severity of the symptom. PMS and PMDD diagnoses were established accordingly. (1) First, symptom cyclicity was defined. The definition of symptom change from follicular to the luteal phase was based on individual statistical tests. Symptom scores from 9 mid-follicular days (cycle days 4–12) were compared with 9 late-luteal phase days (cycle days −1 to −9) by use of Wilcoxon matched-pair, signed-rank test, and a p value less than .05 was required for each individual subject and each symptom [15]. (2) Symptom scores displaying statistically confirmed cyclicity were checked manually to ensure at least a 100% increase in negative and somatic symptoms during the nine last premenstrual days. (3) Finally, mean symptom scores had to exceed a score of 4.0 during the last seven days of the premenstrual phase. According to the above criteria for symptom cyclicity, PMS patients were required to display at least one affective symptom and one somatic symptom, whereas PMDD patients were required to display at least five symptoms (at least four of them being affective symptoms).

As symptom cyclicity is often perceived by the women as PMS, we also assessed symptom cyclicity. For this evaluation, only the cyclicity criterion was used.

2.3. Hormone assays

Progesterone serum concentration was analyzed on Immulite 1000 (DPC, Los Angeles, CA, USA). Progesterone intraassay coefficient of variation was 16% at 2.9 nmol/L and 6.3% at 25.1 nmol/L.

2.4. Statistical analyses

Because two different groups of women with adverse mood during ongoing or prior COC-treatment, with their respective control groups, were recruited, independent *t* tests and chi-square tests were used for the analyses. For non-normally distributed data, Mann–Whitney *U* test was used. Data are presented as mean±S.E.M., unless otherwise stated.

3. Results

Three women in the pCOC-fine group never returned their daily symptom scores. These women have been kept

Table 1
Sociodemographic and clinical variables in the four study groups

	COC-fine (*n*=30)	COC-mood (*n*=28)	pCOC-fine (*n*=27)	pCOC-mood (*n*=33)
Age, years	24.6±2.1	24.8±2.7	26.0±3.9	25.2±2.9
Parity, children	0	1 (3.6%)	2 (7.4%)	3 (9.1%)
Legal abortions, n	0	1 (3.6%)	2 (7.4%)	7 (21.2%)[a]
BMI, kg/m^2	21.6±2.1	21.1±2.2	22.9±3.2	21.7±3.8
Married/cohabiting, n	20 (66.7%)	21 (75.0%)	14 (51.9%)	24 (71.7%)
Students, n	27 (90.0%)	21 (75.0%)	18 (66.7%)	30 (90.9%)
Alcohol use, median g/week (range)	50.0 (0–172)[b]	25.0 (0–115)	37.5 (0–238)	35 (0–172)
Smokers, n	3 (10.0%)	1 (3.6%)	2 (7.4%)	3 (9.1%)

[a] Significantly different from all other groups, p<.05, binary logistic regression.
[b] Significantly different from COC-mood, p<.01, Mann-Whitney U test.

in the analyses as far as possible. All pCOC subjects were considered to have had ovulatory cycles when evaluated, which was also confirmed by progesterone levels >15.0 nmol/L.

The sociodemographic and clinical variables of the study groups are displayed in Table 1. Women who had discontinued COC use due to adverse mood symptoms had a significantly higher frequency of previous legal abortions than any of the other groups.

Similar prevalence rates for any psychiatric disorder (any mood disorder and/or any anxiety disorder) were found among ongoing users of COC with current reports of adverse mood symptoms and among previous users with a history of COC-induced adverse mood (Table 2). Mood disorders were significantly more common in both the COC-mood and pCOC-mood groups in comparison with their control groups (Table 2). Prevalence of any anxiety disorder did not differ between the four groups (Table 2).

Self-reported PMS was significantly more common in the COC-mood and pCOC-mood groups compared with their control groups (Table 3). There was no difference in prospectively defined PMS or PMDD between the pCOC-mood and pCOC-fine groups (Table 3). Affective symptoms reported by women who fulfilled criteria for PMS are displayed in Fig. 1.

4. Discussion

The major finding in this study is that psychiatric disorders such as depression and anxiety are common in women who report adverse mood effects from current or previous COC use. Almost one third of women with ongoing or prior experience of COC-induced mood deterioration fulfilled criteria for any mood and/or any anxiety disorder.

Because of the cross-sectional design of the study, we are unable to determine whether the mood and anxiety disorders found in our ongoing COC users were drug-related, coexisting or preexisting. However, prior users with experience of COC-induced adverse mood had equally high prevalence rates of anxiety and depression as the ongoing users with adverse mood reports, although they were currently not exposed to COCs. If the revealed depression and/or anxiety disorders in ongoing users were entirely COC-related, it could be assumed that the prevalence of depression and anxiety would have been lower in prior users, i.e., women would have recovered from their depression when COC use was discontinued.

Given the high prevalence of mood and anxiety disorders among women with reports of adverse mood

Table 2
Prevalence of any depressive and/or anxiety disorders in women with ongoing or previous use of COCs and with different experiences of adverse mood effects

	COC-fine (*n*=30)	COC-mood (*n*=28)	pCOC-fine (*n*=27)	pCOC-mood (*n*=33)
Any psychiatric diagnosis	3 (10.0%)	8 (28.6%)	2 (7.4%)	11 (33.3%)[a]
Any mood disorder	0	4 (14.3%)[b]	0	7 (21.2%)[a]
Major depressive disorder	0	1 (3.6%)	0	2 (6.1%)
Minor depressive disorder	0	3 (10.7%)	0	5 (15.2%)
Any anxiety disorder	2 (6.7%)	6 (21.4%)	2 (7.4%)	5 (15.2%)
Obsessive–compulsive disorder	0	1 (3.6%)	1 (3.7%)	2 (6.1%)
Generalized anxiety disorder	1 (3.3%)	3 (10.7%)	0	2 (6.1%)
Panic disorder	0	1 (3.6%)	0	1 (3.0%)
Social phobia	1 (3.3%)	2 (7.1%)	1 (3.7%)	3 (9.1%)
Other psychiatric disorder				
Bulimia nervosa	1 (3.3%)			

Some women had more than one diagnosis.
[a] Significantly different from pCOC-fine, p<.05, chi-square test.
[b] Significantly different from COC-fine, p<.05, chi-square test.

Table 3
Prevalence of self-reported PMS and prospectively defined symptom cyclicity, PMS and PMDD

	COC-fine (*n*=30)	COC-mood (*n*=28)	pCOC-fine (*n*=27)[d]	pCOC-mood (*n*=33)
Self reported PMS	10 (33.3%)	18 (64.3%)[a]	13 (48.1%)	27 (81.8%)[b]
Duration of PMS, years (range)	4 (0–8)	5 (0–15)	7 (0–11)	6 (0–14)
Contacted physician for PMS	0	3 (16.7%)	0	1 (3.7%)
Received treatment for PMS	0	1 (5.6%)	0	3 (11.1%)
Significant luteal worsening of at least five symptoms	1 (3.4%)	4 (14.8%)	5 (20.8%)	13 (39.4%)
Prospective PMS[c]			4 (16.7%)	7 (21.2%)
Prospective PMDD[c]			0	2 (6.1%)
State anxiety	50.5±0.4	50.5±0.4	50.9±0.6	50.8±0.5
Trait anxiety	50.3±0.3	49.8±0.4	50.2±0.4	50.3±0.3

[a] Significantly different from COC-fine, p<.05, chi-square test.
[b] Significantly different from pCOC-fine, p<.05, .05, chi-square test.
[c] PMS and PMDD diagnoses according to *DSM-IV*; however, diagnoses are provisional as prospective ratings were only recorded for 36 days. Only prior COC users were evaluated.
[d] Prospective ratings were available in 24 of 27 pCOC-fine subjects.

symptoms from COC use, greater efforts should be made to diagnose, evaluate and treat depression and anxiety in women. According to our findings, the appropriate treatment for many of these women might be antidepressant therapy rather than discontinuation of COC use. The findings of our study are also supported by prior findings

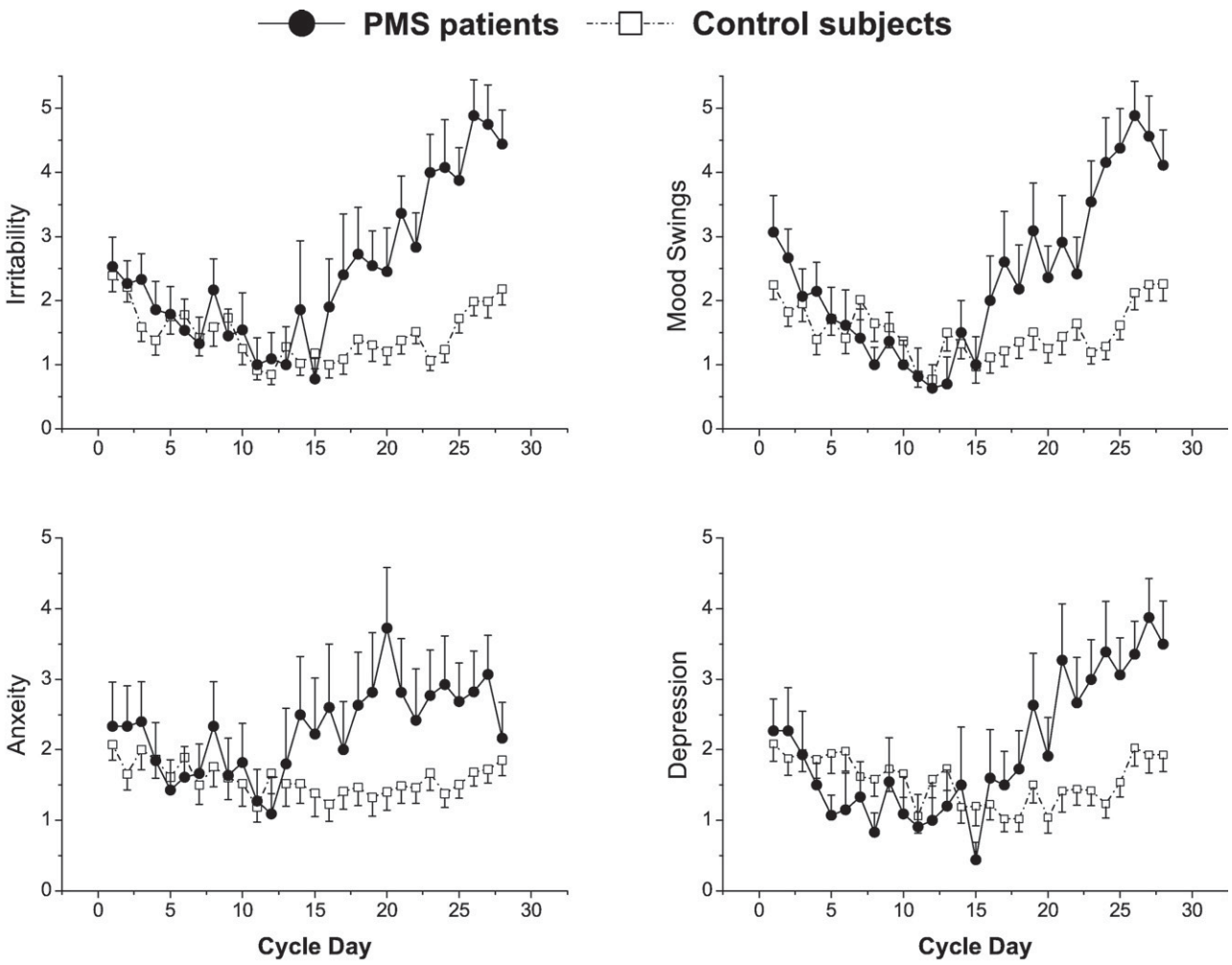

Fig. 1. Confirmatory daily symptom ratings on a nine-point Cyclicity Diagnoser Scale of irritability, mood swings, anxiety and depression scores during an idealized 28-day menstrual cycle. Each point represents the mean±S.E.M. of 11 women who fulfilled provisional prospective criteria of premenstrual syndrome and the remaining 49 previous COC users (denoted as control subjects).

in COC users where a history of depression was found to be significantly associated with mood deterioration during COC use [1].

Clearly, there is an imminent need for prospective studies on adverse mood effects of COCs to elucidate the relation to a given contraceptive brand. In future studies, subjects should preferably be followed prospectively with subjective ratings before start of COC use and only those deteriorating during treatment should be labeled as suffering from adverse mood effects. With such a study design, it would be possible to identify subjects who deteriorate due to the COC and exclude subjects who already, before start of COC use, have a pre-existing psychiatric disorder. For the purpose of this exploratory study, a longitudinal design was considered unsuitable. Given the fact that most women report unchanged or improved mood during COC use, approximately 200 subjects would have to be screened in order to identify a sufficient sample of women with adverse mood.

Self-reported PMS was significantly more common in the two groups with adverse effects of COC compared to their respective control groups. However, when PMS or PMDD diagnoses were verified by use of daily prospective ratings, no differences between the groups were found. Even though the sample size was small, it is unlikely that a larger sample would have yielded a different result. Our finding that PMS/PMDD is not more prevalent among COC users with adverse mood effects is at odds with a previous study where women who had been prospectively defined as suffering from PMS were more prone to report negative mood while on COCs [7]. On the other hand, our finding is in line with previous studies indicating that COCs can be beneficial for women with premenstrual mood symptoms, in particular, if symptoms start at an early age [1]. Recently, it has also been suggested that treatment with a low-dose ethinylestradiol and drospirenone-containing COC is beneficial for PMDD [16,17].

Another important finding of this study was that women who had discontinued COC due to adverse mood effects had a significantly higher frequency of previous legal abortion. Women who discontinue use of COCs due to adverse mood effects often do so, in spite of their ongoing need of contraception. Among women seeking legal abortion, almost 60% stated that they had hesitated to use intrauterine devices and COC, although they had had access to either of those contraceptive methods [18]. The main reasons given why contraception had not been used around the time of conception were adverse experience, a general disliking of hormones and concerns about long-term side-effects [18]. Clearly, counselors need to respond to the women's own definition of her situation, and provide her with adequate contraceptive alternatives [18]. For this reason, counselors need experience with a broad repertoire of contraceptive methods, including the nonhormonal options that are available.

In conclusion, this study has indicated that depression and anxiety are common in COC users with ongoing and previous experience of adverse mood symptom from COCs. Future studies are needed to confirm causal relationships between mood symptom and COC use.

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