



PERGAMON

Psychoneuroendocrinology 28 (2003) 751–766

www.elsevier.com/locate/psyneuen

PNEC

Estrogen fluctuations, oral contraceptives and borderline personality

M. Catherine DeSoto ^{a,*}, David C. Geary ^b, Mary K. Hoard ^b,
Melanie S. Sheldon ^b, Lynn Cooper ^b

^a *Department of Psychology, University of Northern Iowa, Cedar Falls, 50614-0505 IA, USA*

^b *University of Missouri at Columbia, Columbia, MO, USA*

Received 22 January 2001; received in revised form 15 July 2002; accepted 22 July 2002

Abstract

Results from three studies suggest fluctuation in estrogen level may influence the expression of borderline personality disorder (BPD) symptoms. In the first study, 226 women were administered the Personality Assessment Inventory, borderline scales (PAI-BOR; L.C. Morey, *The Personality Assessment Inventory, Professional Manual*, 1991) and a questionnaire that assessed time in menstrual cycle and use of oral contraceptives, that is synthetic estrogens. BPD symptoms were most common in women using oral contraceptives and during times in the menstrual cycle when estrogen level is rising. In Study 2, 52 women were measured four times across one menstrual cycle and provided salivary samples at each test session. The samples were assayed and estrogen levels were obtained. The principle finding was that variation in estrogen levels predicted the presence of BPD symptoms ($r=0.4$, $p<0.01$). This relationship remained significant when a general increase in negative affect was statistically controlled. Study 3 employed a pre–post Oral Contraceptive (OC) design with a control group. It was found that for women with high pre-existing levels of BPD, symptoms became significantly worse after starting pill use ($F(3,42)=4.7$; $p<0.01$). Research findings that link the serotonin system and estrogen are reviewed and theoretical and practical implications are discussed.

© 2003 Elsevier Science Ltd. All rights reserved.

Keywords: Estrogen; Serotonin; Borderline personality disorder; Sex differences

* Corresponding author..

E-mail address: cathy.desoto@uni.edu (M.C. DeSoto).

Estrogen has been shown to be related to a myriad of behavioral and cognitive patterns, especially those known to differ as a function of sex (see Kimura, 1999 for a review; Geary et al., 2002). Borderline Personality Disorder (BPD) is more common among women and thus an influence of female hormones on the expression of associated symptoms is possible, but has not been empirically investigated. The higher prevalence among women (DSM-IV, 1994) coupled with a life history pattern that suggests increased BPD symptoms during adolescence and the perimenopausal years (Stone, 1992; Bardenstein and McGlashen, 1988)—times of rapid hormonal change—are consistent with a hormonal influence on the expression of BPD symptoms. For example, Myers et al., (1993) found that 47% of inpatient adolescent females and none of the males met DSM criteria for BPD. Grilo et al. (1996) found that male and female adolescent inpatients differed in the prevalence of BPD, and that the prevalence of no other personality disorder nor demographic variables were significantly different for males and females in this age-group. Similarly, when persons suffering from BPD are compared in their late forties and early fifties—again a time of hormonal change for women—the functioning of women is significantly worse than that of men, but this sex difference is not found for persons suffering from BPD in their thirties and early forties (Bardenstein and McGlashen, 1988).

When considering a potential relation between sex hormones and behavior, change and rate of change, as well as absolute level of the sex hormone, are potential moderating factors in the expression of the behavior (see also Vliet, 1997; Frank, 2000). If absolute levels of a hormone affect some neural system, fluctuating levels of the hormone could have an especially pronounced effect if the hormone exerts part of its effect via up- and down-regulation of one or more neurotransmitter receptors. Importantly in this regard, estrogen has been shown to increase receptor density of various monoamine receptors (Fink et al., 1996). Although there are other potential mechanisms, one potential link between estrogens and BDP is the serotonin system. Because estrogen is known to affect the serotonin system, and because problems within the serotonin system have been identified in persons with BPD, it is possible that estrogen, and in particular changes in estrogen levels, influence these systems and the expression of BDP. Estrogen has been shown to influence the functioning of the serotonin system (Joffe and Cohen, 1998; Robinow et al., 1998; Bethea et al., 1998). For example, serotonin and the principal metabolite of serotonin, 5-HIAA, are higher during high estrogen phases of the cycle (Fludder and Tonge, 1975), increases in 5-HIAA following estrogen replacement therapy have been reported (Lippert et al., 1996; Mueck et al., 1997), and Bethea and colleagues (see Bethea et al., 1998 for a review) have demonstrated estrogen's influence on the function on both afferent and efferent serotonin neurons as well as receptor sites.

1. Borderline personality disorder

Approximately 2% of the general population has Borderline Personality Disorder (BPD) at any given time (DSM-IV, 1994). Furthermore it seems likely that non-clinical populations are often affected by borderline traits and thus show related

impairment, although to a lesser extent than clinically diagnosed populations (Trull et al., 1997). Persons who have this disorder are markedly unstable in terms of employment, education, relationship patterns and self-image. Those suffering from the disorder are generally quite impulsive, and self-mutilation and suicide attempts are not uncommon. In fact, it is estimated that nearly 10% of those with BPD will end their own life (DSM-IV, 1994).

1.1. Etiology

BPD and the factors that modify its expression are not fully understood, although several etiological factors have been identified. Factors that have received empirical support include childhood trauma (Zanarini and Frankenburg, 1997), genetic factors, and neurochemical abnormalities. At the genetic level, a large-scale twin study suggested that the heritability estimate for BPD may be as high as 0.62 (Torgersen et al., 2000). Neurochemically, a disruption in the ability to utilize and respond to serotonin may be associated with BPD, as described below (deVegvar et al., 1994). Although the etiology is almost certainly multifactorial, the focus of the present research is on the role that biological factors, particularly estrogen fluctuation, may play in the expression of BPD.

The prolactin responses of males with BPD are reduced compared to normal controls and to those with other personality disorders (Coccaro et al., 1989; Trestman et al., 1992), suggesting that reduced responsiveness in the serotonin system may be a hallmark of BPD. Although serotonin response is usually found to be reduced in patients with BPD, most of the biological studies of BPD have focused on men, even though the majority of those diagnosed with the disorder are women (Martial et al., 1997). In challenge studies where women are included, women who have BPD do not always show the blunted response that is typical with men (Hollander, 1994). Indeed an unusually *rapid* response within the serotonin system has been demonstrated among women with BPD in at least one fenfluramine challenge study in which control for estrogen effects was attempted by measuring all women during the post-ovulatory phase of the menstrual cycle (Martial et al., 1997).

1.2. Summary of hypothesis rationale

It is hypothesized that the expression of BPD symptoms, although certainly influenced by a wide variety of factors, may be moderated by rapid fluctuations in estrogen. Supporting this hypothesis is the finding that BPD is more common among women and that the sex difference begins with the cyclical pattern of estrogen levels associated with the reproductive years and is largest during times of relatively greater hormonal flux. The sex difference in male and female serotonin systems and the observation that serotonin systems may be maladaptive in those with BPD make the hypothesis more appealing, in that serotonin may provide a plausible vehicle for estrogen to moderate the expression of BPD symptoms. To summarize, we propose that rapid changes in estrogen will relate to the expression of borderline symptoms in women. This leads to several testable hypotheses. One, individual women whose

monthly cycles are marked by relatively greater fluctuations would be expected to show more BPD symptoms. Two, given that estrogen change is highest during week 2—that is a time of high estrogen preceded by a time of low estrogen—this time should be associated with increases of BPD symptoms. Finally, the use of exogenous hormones which increase the daily fluctuations of estrogen levels—as occurs with oral contraceptives—would be expected to result in some increase in BPD symptoms. It should be noted that ingestion of oral contraceptives (OC) suppresses ovulation and normally occurring monthly hormone fluctuations, but does increase variation in hormone levels on a daily basis. There is a sharp peak in estrogen levels approximately two hours after the ingestion of each pill and a low point about 22 hours later (Beck et al., 1980).

2. Study 1

The first of three studies examined the relation between BPD symptoms and (a) the use of hormone-based birth control, and (b) phase of menstrual cycle in a between-subjects design. If estrogen relates to BPD symptoms, then use of oral contraceptives (OC) should be associated with more severe symptoms, and BPD symptoms should be higher during times of rising estrogen, that is during the second week of the menstrual cycle.

2.1. Methods

2.1.1. Participants

The participants were 226 women (mean age=19 years) from general psychology courses at the University of Missouri at Columbia. The participants received partial course credit for their participation in the study and all participants gave informed consent. All studies reported were approved by an Institutional Review Board. The women were not screened for the presence or absence of psychopathology, however, with a sample this size, it might be expected that some participants would meet the diagnostic criteria of BPD, and a significant number would be experiencing clinically significant levels of symptoms.

2.1.2. Questionnaires

Symptoms of BPD were assessed by self-report using the Personality Assessment Inventory—Borderline Features Scale (PAI-BOR; Morey, 1991). The PAI-BOR is considered to provide a valid assessment of BPD symptoms for non-clinical, as well as clinical populations (Trull, 1995). In addition to providing an index of the overall frequency of BPD symptoms, the measure provides sub-scales for four symptom clusters: identity problems, affective instability, negative relationships, and self-harm. The identity problems sub-scale measures fears of abandonment and malleability of self-image, whereas affective instability measures sudden shifts in mood and intensity of emotion. The negative relationship sub-scale focuses on feelings of betrayal, loneliness, and instability in relationships, whereas the self-harm sub-scale focuses on

impulsive and reckless behavior. Morey's (1991) rule that 36 or more symptoms on the PAI-BOR is indicative of significant borderline symptoms was used to classify the level of symptomology. A separate questionnaire assessed the average length of participants' menstrual cycle, the number of days since the first day of their most recent period, and, whether or not they were using birth control pills or any other form of hormone-based method of birth control.

Women were divided into categories based on their cycle day.¹ On the basis of typical patterns of estrogen fluctuation across the menstrual cycle (Ferlin et al., 1993), day 0 to day 3 and day 26 to day 29 were coded as Low Estrogen ($n=55$). Day 5 to day 10 were coded as Rising Estrogen ($n=49$), and day 11 to day 14 were coded as High Estrogen ($n=25$). Although estrogen rises again around day 18 to day 20, and remains relatively high until about day 24, this time is also marked by high levels of progesterone. Progesterone itself has many effects on mood and cognition. For example, progesterone tends to depress mood while estrogen alone does not (Girdler et al., 1999). Thus, to reduce the potential confounding of estrogen and progesterone levels, women who reported themselves to be between day 15 and day 25 in their cycle ($n=129$) were not included in the associated analyses.

The few participants (less than 5%) who did not answer an item were discarded from the associated analyses and thus there is some variation in the various inventory sample sizes.

2.2. Results

Women who were using OC showed significantly higher levels of borderline symptoms, $F(1, 192)=8.48$, $p<0.01$, than did women not using hormones and menstruating normally. The difference in overall borderline symptoms was largely due to a difference on the negative relationship, $F(1, 196)=13.2$, $p<0.001$, and emotional instability, $F(1, 196)=4.8$, $p<0.05$, sub-scales.

The proportion of women with clinically significant borderline features (i.e., overall PAI-BOR scores >36 ; Morey, 1991) were compared across the three groupings. The results revealed that 17 of the 49 (35%) women in the rising subgroup endorsed clinically significant levels of BPD symptoms, as contrasted with only 5 of the 20 (20%) women in the high subgroup. Women at low estrogen phases were least likely to report significant borderline features (8 of the 55, or 15%). The difference between the rising and low estrogen group was significant, ($\chi^2=5.8$, $p<0.05$) whereas the difference between low estrogen and highest- absolute-level of estrogen group was not ($\chi^2=0.4$, $p>0.4$).

¹ Based on each woman's reported average cycle length and the number of days since the beginning of her last reported menstrual cycle, each woman's day in cycle was estimated. Each woman's cycle was standardized to an average 28 day cycle by dividing the number of days since the first day of her last menstrual period (LMP) by the reported cycle length and then multiplying the quotient by 28. For instance, if a woman reported a cycle length of 30 days and reported it had been 15 days since the first day of her most recent period, her cycle day was coded as 14 (half-way through a standard 28 day cycle).

2.3. Discussion

Study 1 yielded two potentially important findings. First, women using hormone-based birth control showed elevated BPD symptoms, relative to women not taking hormones. Second, BPD symptoms were more common in women assessed on cycle days during which estrogen generally rises relative to women assessed on other cycle days. This suggests that rising or changing levels of estrogen may have more of an influence on BPD symptoms than absolute levels. Of course, the first finding might be due to pre-pill-use differences among the groups of women who were or were not using OC. This question was addressed directly in Study 3.

3. Study 2

The primary goal of Study 2 was to employ a within-subjects design to explore further the potential relation between fluctuations in estrogen levels and BPD symptoms and to do so by directly measuring estrogen levels via salivary assay four times across one month. In addition to estradiol assays, the assessments included the PAI-BOR as in Study 1, as well as questions from three of the nine sub-scales (hostility, depression and anxiety) of the Brief Symptom Inventory (BSI; Derogatis and Melisaratos, 1983). The BSI items were included as covariates to address the possibility that absolute or variable levels of estradiol are actually related to negative affect, rather than to BPD symptoms per se.

If BPD symptoms are exacerbated by fluctuations in estrogen levels, then variability in estradiol level across the month should be positively correlated with PAI-BOR symptoms. Moreover, the change in estradiol level during the time of sharpest increase—cycle-week one to cycle-week two—should be positively related to BPD symptoms. On the other hand, if absolute level of estrogen is related to BPD traits, then we would expect to find a correlation between absolute levels of estrogen and PAI-BOR scores.

3.1. Methods

3.1.1. Participants

The participants were 57 women (mean age=20.1 years) who received partial course credit for participation. Potential subjects were identified by their responses to a pre-testing questionnaire that was administered to all students enrolled in general psychology. Women who were not taking hormones of any kind and having normal menstrual cycles were contacted by means of electronic mail and invited to participate. All women who agreed to participate signed informed consent and were debriefed at the end of the study.

Data from 5 of the 57 women who participated in the study were discarded, because once the study began they reported irregularities in their menstrual cycle. Of the remaining 52 participants, 31 participated in all four sessions and provided adequate saliva samples at each session, whereas 21 women missed one of the four

sessions or did not provide an adequate saliva sample on one occasion. As a result, estradiol measures were only available for three sessions for these 21 women, and thus the *df* differ across some of the analyses reported below.

3.1.2. Saliva collection

Participants were instructed to salivate by passive drool into a polypropylene funnel connected to a cryovial. The sample was unstimulated and the participants allowed all saliva to be collected without interruption for a period of three minutes. Samples were frozen within the hour, and later assayed by an independent laboratory for salivary estradiol (Salimetrics, State College, PA); the procedure was a double antibody radioimmunoassay developed and recently validated at the Penn State Behavioral Endocrinology Laboratory (see Shirtcliff et al., 2000).

To test the hypothesis that variability in estradiol level is related to severity of BPD symptoms, variance scores for estradiol and the PAI-BOR were computed for each participant. As an example, if a woman's salivary assays resulted in 1.1, 0.51, 1.27, and 0.81 pg/ml across the four weeks, the associated variance for these scores was 0.084.

3.2. Results

Each woman's data was aligned based on her reported day in menstrual cycle and the averages can be seen in Table 1. Estradiol levels show the expected pattern of fluctuation: low levels early in the cycle that increase and then decrease ($F(3,90)=11.07, p<0.0001$).² Subjects began the study at various points in their cycle. When the estrogen levels were analyzed by session number (that is unaligned and random with respect to point in menstrual cycle), there was no difference in estrogen levels from one hormone session to the next, as expected ($F=1.53; p>0.2$). Overall these statistics serve to validate alignment procedures.

Table 1
Day in menstrual cycle and average estradiol levels

	Day since beginning of cycle		Estradiol levels (pg/ml)	
	M	SD	M	SD
Week in cycle				
Week 1	4	3	0.30	0.36
Week 2	11	4	0.62	0.54
Week 3	18	5	0.78	0.54
Week 4	26	6	0.72	0.60

² This participant was closely monitored for additional difficulty and referred to the university counseling center. We verified that she made contact with a professional counselor. To our knowledge, she made no further suicidal gestures.

3.2.1. Absolute values and week two changes

The relation between estradiol level and PAI-BOR scores was first examined by means of zero-order correlations for each cycle week. Next, hierarchical regression analyses were computed, whereby the estradiol variable of one cycle week was entered first followed by the estradiol variable for the following week. The zero-order correlation provides an assessment of the relation between *absolute* estradiol levels and the variable in question, whereas the regression analysis provides an assessment of the relation between relative change in estradiol between one week and the next. As an example of the latter, a participant's overall average PAI-BOR score (averaged across the four weeks the survey was completed) would serve as the dependent variable and the estradiol variables for week one and week two as the independent variables. The beta coefficient for the week two variable would then represent the relation between overall PAI-BOR scores and change in estradiol level from week one to week two. On the basis of the predication that rising estradiol levels are associated with increases in borderline symptoms, the week-two beta coefficient for the just described regression analysis was tested using a one-tailed *t*-test. All other week-to-week assessments were evaluated using a 2-tailed *t*-test.

The correlations between the weekly estradiol variables and overall PAI-BOR scores and sub-scale scores ranged between -0.22 (week-one estradiol and overall scores, $df=44$, $p=0.13$) and 0.19 (week-two estradiol and negative relationship, $df=43$, $p>0.20$), and none of these were significant, providing no support for the hypothesis that absolute level of estrogen predicts BPD symptom severity.

The regression analyses revealed one consistent pattern: A sharp rise in estradiol level from week one to week two was associated with higher overall borderline symptoms, $\beta=0.41$ [$t(1,36)=2.08$, $p<0.025$, 1-tailed], as predicted. There was a corresponding tendency toward higher symptoms for each of the sub-scales; negative relationships, $\beta=0.33$ [$t(35)=1.52$, $p<0.07$, 1-tailed], emotion, $\beta=0.37$ [$t(35)=1.70$, $p<0.05$, 1-tailed], self-harm, $\beta=0.38$ [$t(38)=1.99$, $p<0.03$, 1-tailed] and identity, $\beta=0.33$ [$t(36)=1.54$, $p<0.07$, 1-tailed]. None of the other week-to-week regression analyses revealed a significant relation between change in estradiol level and PAI-BOR scores ($ps>0.10$).

3.2.2. Variability in estradiol and BPD symptoms

In keeping with the specific hypothesis that variation in estrogen levels may worsen BPD traits, the variability variable for estradiol was significantly correlated with overall PAI-BOR scores [$r(38)=0.45$, $p<0.01$], and to three of the four sub-scales: emotional instability [$r(37)=0.44$, $p<0.01$]; negative relationships [$r(37)=0.40$, $p<0.05$]; identity problems [$r(37)=0.38$, $p<0.05$]; and, for self-harm was not significant [$r(38)=0.17$, $p>0.25$].

To determine if the effect of estrogen on borderline symptoms could be explained by a more general tendency to endorse negative items, and thus not specific to borderline features, the BSI scores for depression, hostility, and anxiety were all entered as covariates in a hierarchical regression analysis, followed by the average score on the PAI-BOR. The estradiol variance variable still accounted for a significant amount of variance in overall borderline symptoms [$\beta=0.26$ [$t(32)=2.07$, $p<0.05$].

3.3. Discussion

The data support the idea that variability and change in estradiol levels may be related to borderline symptoms, whereas absolute levels are not. Importantly, the changes in estrogen level seem to contribute unique variance to the expression of BPD, variance not attributable to more general factors, as the pattern held when BSI scores for depression, hostility, and anxiety were all statistically controlled.

4. Study 3

The third study was designed to determine if hormone administration causes an increase in BPD symptoms using a quasi-experimental design. In this study, women who indicated they were going to start using birth control pills were assessed four times in the month before beginning OC and four times after they began taking OC. Another group of women who were not planning to begin taking OC were tested four times across one month, and four times across the subsequent month as well.

Although a higher level of symptoms was observed among women who were using OC in Study 1, the interpretation of a within-subjects design as in Study 3 is less susceptible to alternative explanations, and the hypothesis that women who take OC have pre-existing differences compared to women who do not take OC can be directly tested. Here, it was hypothesized that women who commence taking OC will show an increase in symptoms of BPD, not explainable due to pre-existing differences. Second, it was hypothesized that women who are already high on symptoms of BPD will show a more marked increase in BPD symptoms with the onset of OC use. This second hypothesis arises from the conjecture that some persons who have BPD have a pre-existing problem with their serotonin system (Coccaro et al., 1989; Martial et al., 1997). Because the serotonin system is affected by estrogen on a variety of levels (Betha et al., 1998), daily ingestion of estrogen containing OC could potentially exacerbate a pre-existing problem.

4.1. Methods

4.1.1. Participants

The experimental group consisted of 24 women who were planning to begin OC use in the near future. Of the 24 women, 17 completed the study. Three dropped out after one or two sessions stating they had decided not to participate or that they no longer met selection criteria, perhaps indicating they decided not to start using OC. Four were dropped for missing multiple sessions. The control group consisted of 29 women who were not planning to begin using OC. Six of the 29 missed one of the eight sessions, but were still included in the subsequent analyses.

Participants received a letter of invitation by means of electronic mail if they matched certain selection criteria based on their responses to a pre-screening questionnaire administered to all students taking general psychology at the University of Missouri. Furthermore, the pre-screening questions included questions from the

relationship sub-scale of the PAI-BOR. Women who scored higher on the relationship sub-scale of the PAI-BOR were invited first, in an effort to increase the number of participants who were in the clinical range of borderline symptomology. All participants received partial course credit for their participation in the study, provided signed consent and were debriefed at the end of the study.

4.1.2. Questionnaires and testing procedures

Participants completed the PAI-BOR, as in Study 1 and Study 2. Women in the experimental group provided a copy of their birth control prescription and were queried about the day they began taking their pills. All women in the experimental group were taking combination-type OC and the dosage of their estrogen per pill ranged from 20 to 40 µg of ethinyl estradiol, or for three participants, 50 µg of mestranol. All participants completed the PAI-BOR eight times (except as noted above). Subjects in the experimental group completed their surveys, one per week for four consecutive weeks and then waited until they began using OC. After they began the use of OC, the experimental participants completed the last four surveys, approximately one week apart, on four consecutive weeks.

4.2. Results

4.2.1. Preliminary analyses

To determine if the two groups were equivalent to begin with, they were compared on their first four sessions' data. Specifically, a mixed ANOVA was conducted on the first four sessions with session as a repeated factor, and plan to begin using OC as a between factor. Here, the lack of a main effect for OC indicates that the two groups did not systematically differ in their pre-existing levels of BPD symptoms ($F(1,41)=0.06$, n.s.)

Next, the control group's average across the last four surveys was compared to the mean of the first four surveys via a dependent *t*-test. The finding of no significant difference ($t(28)=<1$, n.s.) indicates that mean PAI-BOR scores do not typically vary from one month to the next.

A mixed ANOVA was performed with one between factor (group; experimental versus control) and two within factors (pre-OC versus post-OC; session 1 through 8). The non-significant interaction between group (OC versus no OC) and pre versus post (first four sessions versus last four sessions) suggests that, *as a whole*, women who begin use of OC do not show an increase in symptoms ($F(1,36)<1$, n.s.). The remaining interactions were all non-significant as well; pre/post by time ($F(3,108)=1.64$, $p>0.1$); OC by time ($F(3,108)<1$, n.s.); and pre/post by time by group ($F(3,108)=1.01$, $p>0.25$), indicating there were no trends in scores on the PAI-BOR as a function of session time.

4.2.2. High versus low pre-existing symptoms

Participants were divided into two groups, based on their BPD item endorsement across the first four sessions. Participants who scored above the mean were coded as "high BPD" ($n=17$, 12 control, 5 experimental). Women who had an average item

endorsement below the overall mean were coded as “low BPD” ($n=29$, 12 experimental, 17 control). An ANCOVA was conducted with group (OC versus control group) and BPD symptom level (high versus low) as between factors and pre-existing level of BPD symptoms (i.e., the average from the first four sessions) as the covariate. The dependent variable was the post-OC mean on the PAI-BOR (i.e., scores averaged across the last four sessions). The inclusion of pre-existing symptoms as a covariate has the effect of removing the associated variance, thus isolating the change in symptoms following the use of OC from pre-existing symptom levels.

Means and standard deviations for pre- and post-pill use for high- and low-BPD symptom groups are shown in Table 2. Here, the hypothesis that women with high BPD symptoms will worsen after beginning use of OC is tested by the interaction of group by level-of-symptoms. Results suggest that the use of OC has a different effect depending of the level of pre-existing symptoms ($F(1,41)=4.94$, $p<0.05$).

Follow up analyses for simple effects compared the PAI-BOR scores for the women who began taking the pill to the scores of the control group separated as a function of high versus low pre-existing symptoms. Results indicated that among women with lower levels of BPD symptoms, starting the pill had little effect on symptom severity ($F(1,26)<1$, n.s.). Conversely, among women with higher BPD symptoms, starting the pill was associated with an increase in symptom severity ($F(1,14)=3.99$, $p<0.05$, one-tailed) as hypothesized. The nature of this interaction can be seen in Fig. 1, which depicts the nature of the interaction in terms of a difference scores (the average of the last four sessions minus the average of the first four sessions).

In a further test of the possibility that only women with BPD symptoms in the high range will be adversely affected by the daily rise and fall of estrogen levels that occur with OC usage, both a bivariate correlational analysis was performed as well as a multiple regression analysis. First, the Pearson correlation coefficient between level of pre-existing symptoms (the average of the first four sessions) and the amount of change after beginning OC (daily dose of female sex hormones) (i.e., the mean of the four post scores—the mean of the four pre scores) was calculated among the experimental group. Results reveal a significant relationship ($r(15)=0.42$, $p<0.05$, one tailed). The positive correlation suggests that high levels of BPD item endorsement are associated with an exacerbation of symptoms under the influence

Table 2
OC and BPD among women high and low on pre-existing symptoms

	No-pillcontrol group ($n=29$)		Pillexperimental group ($n=17$)	
	Low symptoms	High symptoms	Low symptoms	High symptoms
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Pre-pill PAI-BOR	18 (4.7)	34 (6.0)	17 (4.8)	38 (7.8)
Post-pill PAI-BOR	18 (6.4)	32 (6.5)	17 (5.8)	41 (7.7)

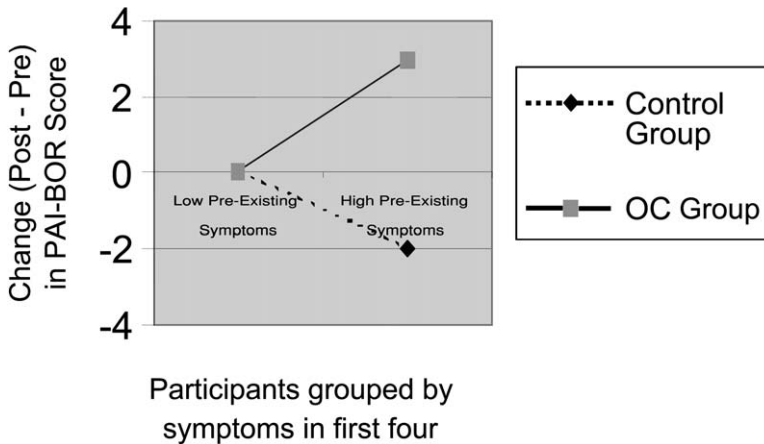


Fig. 1. Difference in PAI-BOR scores.

of estrogen. Among control group participants, the correlation was non-significant and negative ($r(25)=-0.28$, $p<0.15$) indicating a slight trend for women with higher levels of BPD symptoms to score lower on the latter sessions and for women with lower scores to score higher on latter sessions. This trend could be described as a regression toward the mean, and is, of course, the opposite of the pattern seen in the experimental group. Finally, it should be noted that for the experimental group the pattern did not vary with type of OC (monophasic versus triphasic).

4.3. Discussion

As previously explained, it is possible that the serotonergic system may differ for women with BPD relative to other women, and estrogen may exert an influence on BPD via the serotonin system. Thus, if the serotonergic system influences BPD symptoms and is, in turn, influenced by fluctuation in estrogen levels, it seems plausible that estrogen might effect women who have BPD differently than other women. Although the results do not directly address whether the serotonergic system is involved, they do indicate that participants who are higher on BPD symptoms experience an exacerbation of these symptoms when they begin to use OC, whereas other women do not show a change in BPD symptoms. The latter finding is of significant practical import, as it suggests that beginning use of OC does not appear to cause a generalized increase in borderline symptoms among most women, at least in the first month of use.

5. General discussion

The results of Study 1 demonstrated that clinically significant levels of BPD symptoms were more common in women assessed on cycle days during which estrogen

generally rises than in women assessed on other cycle days. The implication is that the rate of change in estrogen levels may influence BPD symptom expression. In Study 1, it was also found that women using hormone-based birth control showed elevated BPD symptoms, relative to other women. Study 2, which directly measured estradiol via salivary assay, demonstrated that variability and change in estradiol level from week one of the cycle to week two of the cycle, a time of rapid rise in estrogen level, were associated with higher levels of borderline symptoms. Again, the results suggest that it is variation and not absolute levels of estrogen that may influence symptoms of BPD. The changes in estrogen levels seem independent of a general increase in negative affect, as the pattern held when the variance associated with depression, hostility, and anxiety were statistically removed.

Study 3 was a follow up of the results of Study 1. Specifically, using a within-subject pre–post pill design and a control group, the results of Study 3 support the hypothesis that the use of OC may cause an increase in BPD symptoms but only among women who have high pre-existing levels of BPD symptomology. It is also important to note that one participant whose pre-OC scores on the PAI-BOR suggested a diagnosis of BPD had a worsening of symptoms after beginning the pill to the extent that she made a suicidal gesture. Specifically, during the second post-OC session, when asked how she was, she replied, “Well, OK I guess, except that I tried to slash my wrists last night.”² She went on to report that she was just feeling terrible, very moody and upset. At least in this one case, the observed increase in symptoms on the PAI-BOR associated with beginning to use the pill co-occurred with a real life indicator of a significant worsening of BPD symptoms.

The role of progesterone was not assessed in these studies. The results of Study 1 and Study 3 which link use of OC to BPD symptoms could be partially explained by the fact that OC also contain progesterone, which as previously noted also affects mood and cognition. Although the results of Study 2 and week in cycle effects of Study 1 suggest the importance of estrogen levels, future research should investigate the possibility that levels of progesterone may be important as well.

The overall pattern suggests that variability in levels of estrogen, rather than absolute levels, seem to better represent the potential relation between estrogen and BPD symptomology. Women, of course, normally vary in the level of estrogen across the menstrual cycle, but the results of these studies suggest that extreme fluctuations in estrogen may be problematic, or that normal fluctuations are problematic for women with BPD tendencies.

It is not clear from these studies, but a mechanism linking estrogen fluctuations, serotonin and BPD symptoms could occur neurochemically via a variety of neural mechanisms, including a series of receptor down-regulations and up-regulations. Down regulation can occur quickly, within one or two hours of a maintained increase in neurotransmitter levels (see Feldman et al., 1997 for a discussion of these processes). Individual differences in serotonin system sensitivity do occur and theoretically may be magnified by estrogen fluctuations; equally plausible is that individual differences in estrogen fluctuation could result in individual differences in serotonin system sensitivity. Such links between the serotonin system and estrogen fluctuation may explain the results of the present studies and also join well with

what is currently known about the relations among the serotonergic systems and estrogens, and the serotonergic systems and BPD. Further studies will, of course, be needed to determine whether or not these links exist.

An important limitation for these studies is the use of non-clinical samples. Given the exploratory nature of the current research, a general cross-section of the population was deemed most appropriate. In doing so the results may have applications to the higher functioning BPD sufferers most likely to use OC, that is women with significant but non-clinical levels of BPD symptoms. Although the sample size would be expected to include a number of women who would meet diagnostic criteria and the self-report measure used is well validated, future studies should address this issue with a larger sample of clinically diagnosed patients and use semi-structured interviews as well as self-reporting of symptoms.

In summary, the present studies report a potential relation between estrogen and symptoms of borderline personality, but do not imply that estrogen itself causes BPD. Rather, the results suggest that in some women fluctuations in estrogen levels appear to aggravate pre-existing BPD tendencies. Although the present findings have limitations, they are of sufficient merit to warrant further investigation into the role of estrogen on the expression of BPD symptoms.

Acknowledgements

We thank Mark Flinn for his advice on salivary collection and Tim Trull for his comments on an earlier version of this paper. We thank Heather Hastings, Maggie Cole, Chattavee Numtee, Matthew Felton, Catherine Ford, Rebecca Gilbertson, Elena Sullivan, and Natasha Lubenko for assistance with data coding and collection. The research was partially supported by a research grant from the graduate school of the University of Missouri awarded to the first author.

References

- American Psychiatric Association 1994. Diagnostic and statistical manual of mental disorders. , 4th ed. American Psychiatric Association, Washington, DC.
- Bardenstein, K.A., McGlashen, T.H., 1988. The natural course of a residentially treated borderline sample: gender differences. *Journal of Personality Disorders* 2 (1), 69–83.
- Beck, L.R., Cowsar, D.R., Pope, V.Z., 1980. Long-acting steroidal contraceptive systems. *Research Frontiers in Fertility Regulation* 3 (1), 139–150.
- Bethea, C.L., Pecins-Thompson, M., Schutzer, W.E., Gundlach, C., Lu, Z.N., 1998. Ovarian steroids and serotonin neural function. *Molecular Neurobiology* 18 (2), 87–123.
- Coccaro, E.F., Seiver, L.J., Klar, H.M., 1989. Serotonergic studies in patients with affective and personality disorders: correlates with suicidal and impulsive aggressive behavior. *Archives of General Psychiatry* 46, 587–599.
- Derogatis, L.R., Melisaratos, N., 1983. The brief symptom inventory: an introductory report. *Psychological Medicine* 13, 595–605.
- deVevar, M.L., Seiver, L.J., Trestman, R.L., 1994. Impulsivity and serotonin in borderline personality disorder. In: Silk, K.R. (Ed.), *Biological and neurobiological studies of borderline personality disorder*. American Psychiatric Press, Washington, DC, pp. 23–40.

- Feldman, R.S., Meyer, J.S., Quenzar, L.F., 1997. Principles of neuropsychopharmacology. Sinauer Associates, Inc, Sunderland, MA.
- Ferin, M., Jewelewicz, R., Warren, M., 1993. The menstrual cycle: physiology, reproductive disorders, and infertility. Oxford University Press, New York.
- Fink, G., Sumner, B.E., Rosie, R., Grace, O., Quinn, J.P., 1996. Estrogen control of central neurotransmission: effect on mood mental state and memory. *Cellular and Molecular Neurobiology* 16 (3), 325–344.
- Fludder, J.M., Tonge, S.R. (1975). Variations in the concentrations of monoamines and their metabolites in eight regions of rat brain during the estrous cycle: A basis for interactions between hormones and psychotropic drugs. *Journal of Pharmaceutical Pharmacology*, 27 (suppl. 2), 39.
- Frank, E., 2000. Gender and its effect on psychopathology. American Psychopathological Association, Washington, DC.
- Geary, D.C., DeSoto, M.C., Hoard, M.K., Sheldon, M.S., Cooper, L.C., 2001. Estrogens and the menstrual cycle: Relation to jealousy patterns and sexual behavior. *Human Nature* 12 (4), 299–320.
- Girdler, S.S., O'Brient, C., Steege, J., Grewen, K., Light, K.C., 1999. A comparison of the effect of estrogen with and with out progesterone on mood and physical symptoms in postmenopausal women. *Journal of Women's Health and Gender Based Medicine* 8 (5), 637–646.
- Grilo, C.M., Becker, D.F., Fehon, D.C., Walker, M.L., Edell, W.S., McGlashen, T.H., 1996. Gender differences in personality disorders in psychiatrically hospitalized adolescents. *American Journal of Psychiatry* 153 (8), 1089–1091.
- Hollander, E., Stein, D.J., DeCaria, C.M., Cohen, L., Saoud, J.B., Skodol, A.E., Kellmen, D., Rosnick, L., Oldham, J.M., 1994. Serotonergic sensitivity in borderline personality disorder: preliminary findings. *American Journal of Psychiatry* 151 (2), 277–280.
- Joffe, H., Cohen, L.S., 1998. Estrogen, serotonin and mood disturbance: where is the therapeutic bridge? *Biological Psychiatry* 44, 798–811.
- Kimura, D., 1999. Sex and cognition. Bradford/MIT Press, Cambridge, MA.
- Lippert, T.H., Filshe, M., Mueck, A.O., Seeger, H., Zwirner, M., 1996. Serotonin metabolite excretion after postmenopausal estradiol therapy. *Maturitas* 24, 37–41.
- Martial, J., Paris, J., Leyton, M., Zweig-Frank, H., Schwartz, G., Teboul, E., Thavundayil, J., Larue, S.N., Ng Ying Kin, N., Vasavan Nair, N., 1997. Neuroendocrine study of serotonin function in female borderline personality patients: a pilot study. *Biological Psychiatry* 42, 737–739.
- Morey, L.C., 1991. The personality assessment inventory: professional manual. Psychological Assessment Resources, Odessa, FL.
- Mueck, A.O., Seefer, H., Kabpohl-Butz, S., Tiechmann, A.T., Lippert, T.H., 1997. Influence of norethisterone acetate and estradiol on the serotonin system of post-menopausal women. *Hormone Metabolism Research* 29, 80–83.
- Myers, W.C., Burkett, R.C., Otto, T.A., 1993. Conduct disorder and personality disorders in hospitalized adolescents. *Journal of Clinical Psychiatry* 54, 21–26.
- Robinow, D.R., Schmidt, P.J., Roca, C.A., 1998. Estrogen–serotonin interactions: implications for affective regulation. *Biological Psychiatry* 44, 839–850.
- Shirtcliff, E.A., Granger, D.A., Schwartz, E.B., Curran, M.J., Booth, A., Overman, W.H., 2000. Assessing estradiol in biobehavioral studies using saliva and blood spots. Simple radioimmunoassay protocols, reliability, and comparative validity. *Hormones and Behavior* 38, 137–147.
- Stone, M.H., 1992. Borderline personality disorder: course of illness. In: Clarkin, J.F., Marziali, E., Munroe-Blum, H. (Eds.), *Borderline Personality Disorder: clinical and empirical perspectives*. The Guilford Press, New York, pp. 67–86.
- Torgerson, S., Lygren, S., Oien, P.A., Skre, I., Onstad, I., Edvarssen, J., Tambs, K., Kringlen, E., 2000. A twin study of personality disorders. *Comprehensive Psychiatry* 41 (6), 416–425.
- Trestman, R.L., Coccaro, E.F., Temple, J., 1992. Impulsivity and serotonin in borderline personality disorder. Paper presented at the 145th Annual Meeting of the American Psychiatric Association, Washington, DC.
- Trull, T.J., 1995. Borderline personality disorder features in nonclinical young adults: identification and validation. *Psychological Assessment* 7, 33–41.
- Trull, T.J., Useda, D., Conforti, K., Doan, B.T., 1997. Borderline personality disorder features in nonclinical young adults: two-year outcome. *Journal of Abnormal Psychology* 106 (2), 307–314.

- Vliet, E.L., 1997. Screaming to be heard: Hormonal connections women suspect and doctors ignore. M. Evans and Co, New York.
- Zanarini, M.C., Frankenburg, F.R., 1997. Pathways to the development of borderline personality disorder. *Journal of Personality Disorders* 11 (1), 93–104.