



Is there a relationship between estrogen serum level and symptom severity throughout the menstrual cycle of patients with schizophrenia?

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Background: Sex differences in terms of age at onset, symptom expression and course of illness have consistently been demonstrated in patients with schizophrenia. Some studies have reported that schizophrenic symptoms are exacerbated during the premenstrual phase when the blood estrogen level is low. Nevertheless, the results are controversial. We hypothesized that higher levels of estrogen would be associated with a decreased severity of illness in women with schizophrenia. To that end, we examined the relation of gonadal hormone levels to severity of symptoms in 30 women with chronic schizophrenia.

Methods: Patients were 30 female in-patients who met Diagnostic and Statistical Manual of Mental Disorders IV criteria for chronic schizophrenia, aged between 20 and 40 years. All patients received a fixed dose of risperidone (6 mg/day) throughout the study and were assessed over one complete menstrual cycle following 1 month's hospitalization. During the second month they were assessed from the first day of menstrual flow to the onset of the next menstrual flow period. A trained resident of psychiatry who was blind to the patients' cycle phase, used the Positive and Negative Syndrome Scale (PANSS) to rate patients. They rated each patient four times during the menstrual cycle: on the third day of menstruation when estrogen and progesterone levels are low; on the tenth day of menstruation when the estrogen level is rising; on the 13th day of menstruation when estrogen level is high (preovulatory peak); and on the 21st day of menstruation (midluteal) when progesterone level is high. Serum levels of estrogen, progesterone and prolactin were measured on the same days. **Results:** A repeated-measures analysis of variance showed a significant change in the serum level of estrogen and progesterone. *Post hoc* Tukey comparisons of the estrogen and progesterone serum levels on day 3 with days 10, 13 and 21, revealed a significant increase ($p < 0.001$). In addition, a repeated-measures analysis of variance showed significant changes on the PANSS total scores and all its subscales including positive, negative and general psychopathology. Regarding PANSS total scores and all its subscales, *post hoc* comparisons of day 3 with the scores on days 10 and 13 by means of the Tukey procedure revealed a significant reduction from day 3 ($p < 0.001$). **Conclusion:** Although more systematic research is needed to understand the etiology of the sex difference in schizophrenia, the present data add to a growing body of research suggesting that estrogen has an important role in the brain and higher estrogen levels in female patients with schizophrenia may be associated with better outcome. Moreover, exacerbation of symptoms during the premenstrual period supports the role of reproductive hormones in schizophrenia.

Sex differences in terms of age at onset, symptom expression and course of illness have been consistently demonstrated in patients with schizophrenia [1–3]. A number of studies have demonstrated that symptoms of schizophrenia are aggravated before or during menstruation [4–6]. In addition, psychiatric admissions increase during these times. Several lines of evidence suggest that psychotic symptoms appear suddenly, before or during menstruation and then resolve after the cessation of menstruation, even in normal women [4–6].

Recently, there have been several reports of a close relationship between estrogen level and severity of psychotic symptoms in schizophrenia. Nevertheless, the results are controversial [7–9]. Exacerbation of symptoms during premenstrual and postpartum periods and the need for higher medication doses in postmenopausal patients suggest an important role of the sex-hormone estrogen in the modulation of psychopathology in schizophrenia [7,10,11]. In addition, anti-dopaminergic properties of estrogen have been demonstrated in animal studies in which

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estrogen reduced dopamine concentrations and dopamine D2 receptor sensitivity in the brain [12].

Before carrying out larger studies on the effect of estrogen in psychotic patients, it is important to understand the existing relationship of estrogen to psychotic symptoms in patients with schizophrenia. We hypothesized that higher levels of estrogen would be associated with decreased illness severity in women with schizophrenia. To that end, we examined the relationship of gonadal hormone levels to severity of symptoms in 30 women with chronic schizophrenia.

Methods

Patients were 30 female in-patients at Roozbeh Psychiatric Hospital, Tehran, Iran who met the criteria for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) chronic schizophrenia [13] and who were aged between 20 and 40 years. Legal guardians of patients gave written informed consent for a study of sex differences and severity of psychotic symptoms. At the first stage of patient selection, a questionnaire was administered regarding menstrual regularity and duration of menstrual flow (days). We then selected 52 patients who reported a regular menstrual cycle for at least 3 months and a menstruation period of 4 to 7 days. Patients with a history of affective disorders were excluded from the study. At the second stage of patient selection, we observed 52 patients over one complete menstrual cycle. Finally, 30 patients who had a regular menstrual cycle length from 25 to 35 days and a menstruation period lasting 4 to 7 days were selected as the subjects for this study. No evidence of medical illness, particularly endocrinologic or gynecologic illness was found on their medical history, physical examination, or hematologic or biochemical laboratory tests.

The first half (approximately 14 days) of the menstrual cycle is the follicular phase. This

phase begins with menstruation and ends with preovulatory peak (approximately day 13), when estrogen levels are highest, and with ovulation (day 14). The next 14 days are the luteal phase, during which progesterone levels slowly rise to a peak at the mid-way point (midluteal) followed by a second, slightly lower peak of estrogen relative to the preovulatory peak. The pre- and postovulatory lower limits of values for normal women were taken from laboratory values of normal women reported in the study of Riecher-Rossler and colleagues [14].

All patients received a fixed dosage of risperidone (6 mg/day) throughout the study and were assessed over one complete menstrual cycle following 1 month's hospitalization. During the second month, they were assessed from the first day of menstrual flow to the onset of the next menstrual flow period. A trained resident of psychiatry who was blind to the patients' cycle phase, used the Positive and Negative Syndrome Scale to rate patients (PANSS) [15]. The PANSS includes 30 items that measure both positive and negative symptoms, as well as general psychopathology by means of a semistructured patient interview. The resident of psychiatry rated each patient four times during menstrual cycle:

- On the third day of menstruation
- On the tenth day of menstruation
- On the 13th day of menstruation (preovulatory peak)
- On the 21st day of menstruation (midluteal)

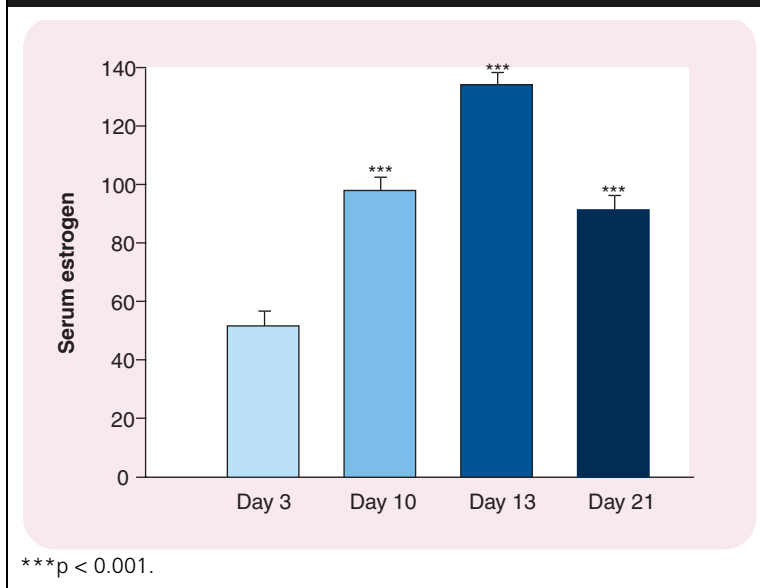
Serum levels of estrogen, progesterone and prolactin were measured on the same days. Blood sampling was carried out in the morning before medication was dispensed. Serum was kept frozen at -70°C . All laboratory analyses were performed in a single batch after all blood samples were collected, to avoid methodologic variation. Serum levels of estrogen, progesterone and prolactin were measured by radioimmunoassay.

Table 1. Demographic and clinical characteristic of 30 female inpatients with chronic schizophrenia.

| Characteristic | Mean | Standard deviation |
|---|-------|--------------------|
| Age (years) (range = 22–38) | 29.06 | 4.77 |
| Duration of illness (years) (range = 3–15) | 7.60 | 3.18 |
| Education (years) (range = 5–12) | 8.66 | 2.36 |
| PANSS Total score at admission (range = 60–119) | 84.60 | 14.49 |

Ethnicity: All Persian; History of abortion: None; Marital status: Single: 19; Married: 9 (all with children); Divorced: 2; PANSS: Positive and Negative Syndrome Scale; Type of menstrual cycle: All regular.

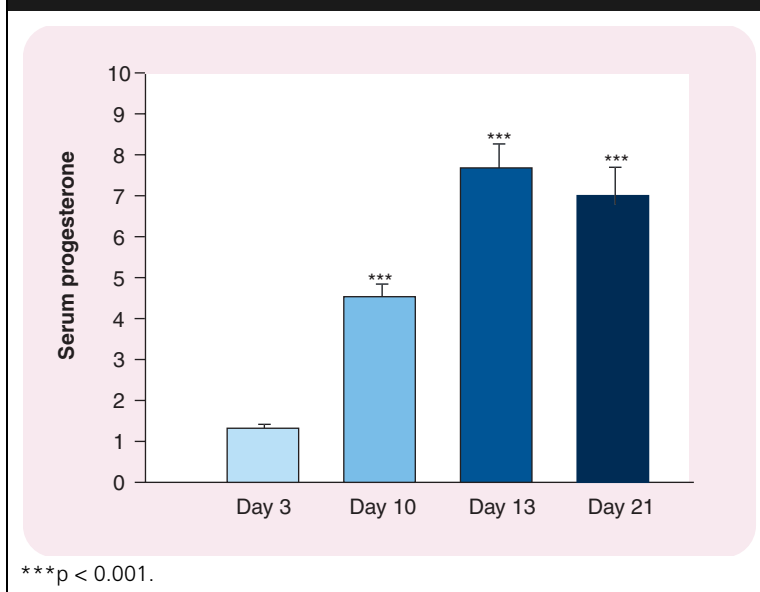
Figure 1. Changes of mean estrogen serum levels over the four stages of the menstrual cycle (days 3, 10, 13 and 21) of all 30 patients with chronic schizophrenia.



Statistical analysis

Mean total PANSS score and mean subtotal scores for each of the positive, negative and general psychopathology subtotals of the 30 patients as well as mean estrogen, progesterone and prolactin levels were compared with repeated measures analysis of variance (ANOVA) between days 3, 10, 13 and 21 of menstruation. When the analysis indicated significant differences, the differences were analyzed

Figure 2. Changes of mean progesterone serum levels over the four stages of the menstrual cycle (days 3, 10, 13 and 21) of all 30 patients with chronic schizophrenia.



with a two-tailed *post hoc* Tukey test. Results are presented as mean ± standard error of the mean (SEM). Differences were considered significant with $p < 0.05$.

Results

Demographic and clinical characteristics of the patients, including age, duration of illness, education, marital status, type of menstrual cycle and PANSS total scores when they entered into the study are shown in Table 1.

Serum level of estrogen

Mean serum levels of estrogen for four menstrual cycle phases are shown in Figure 1. A repeated measures ANOVA showed a significant change in the serum level of estrogen among four stages of the menstrual cycle. *Post hoc* Tukey comparisons of the estrogen serum level on day 3 with days 10, 13 and 21 revealed a significant increase ($p < 0.001$).

Serum level of progesterone

Mean serum levels of progesterone for four menstrual cycle phases are shown in Figure 2. A repeated measures ANOVA showed a significant change in the serum level of progesterone between the four stages of the menstrual cycle. *Post hoc* Tukey comparisons of the progesterone serum level on day 3 with days 10, 13 and 21 revealed a significant increase ($p < 0.001$).

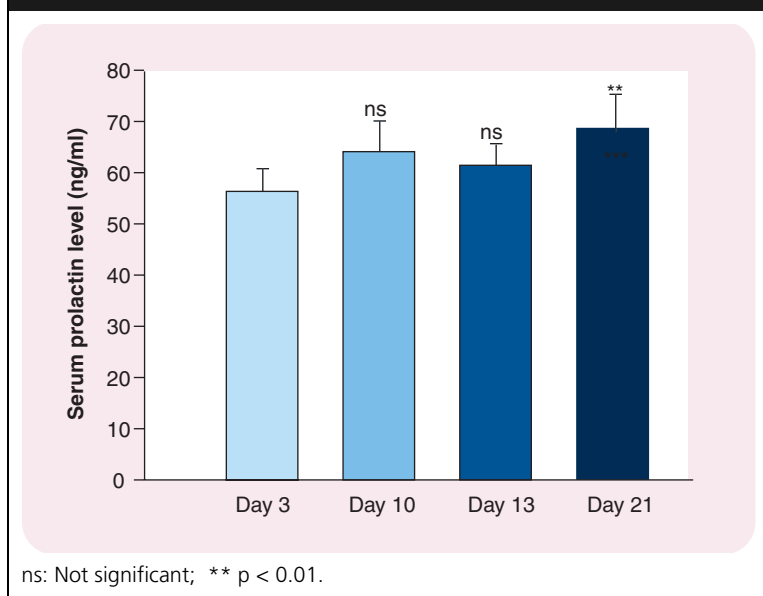
Serum level of prolactin

Mean serum levels of prolactin for four menstrual cycle phases are shown in Figure 3. A repeated measures ANOVA showed a significant change in the serum level of prolactin between the four stages of the menstrual cycle. *Post hoc* Tukey comparisons of the prolactin serum level on day 3 with days 10, 13 and 21 revealed only a significant increase at day 21 ($p = 0.002$).

Positive & Negative Syndrome Scale Scores

The mean ± SEM score of positive, negative and general psychopathology subscales and PANSS total score of patients are shown in Figures 4A–D. A repeated measures ANOVA showed a significant change on the PANSS total scores (Figure 4D) and all its subscales (Figure 4A–C). In PANSS total scores and in all its subscales, *post hoc* comparisons of day 3 with the scores on days 10 and 13 by means of the Tukey procedure revealed a significant reduction from day 3. Comparisons between days 3 and 13 for PANSS scores and estrogen/progesterone serum levels are shown in Table 2.

Figure 3. Changes of mean prolactin serum levels over the four stages of the menstrual cycle (days 3, 10, 13 and 21) of all 30 patients with chronic schizophrenia.



Discussion

Sex hormones play a major role through their effects on central brain neurotransmitters, and may be an important key to the etiology of schizophrenia [3]. The recognition of such hormonal influence during monthly cycles, or at key lifetime hormonal events, such as menopause in women, may also lead to more effective treatment such as preventive estrogen replacement therapy [7]. In this study, the mean total PANSS score and its subscales score for all subjects was significantly different between four menstrual phases, being highest in the premenstrual phase (day 3) and lowest in the postmenstrual phase (day 13). Therefore, this study suggests that higher estrogen levels are associated with lower severity of symptoms of schizophrenia according to PANSS. The findings of this study are

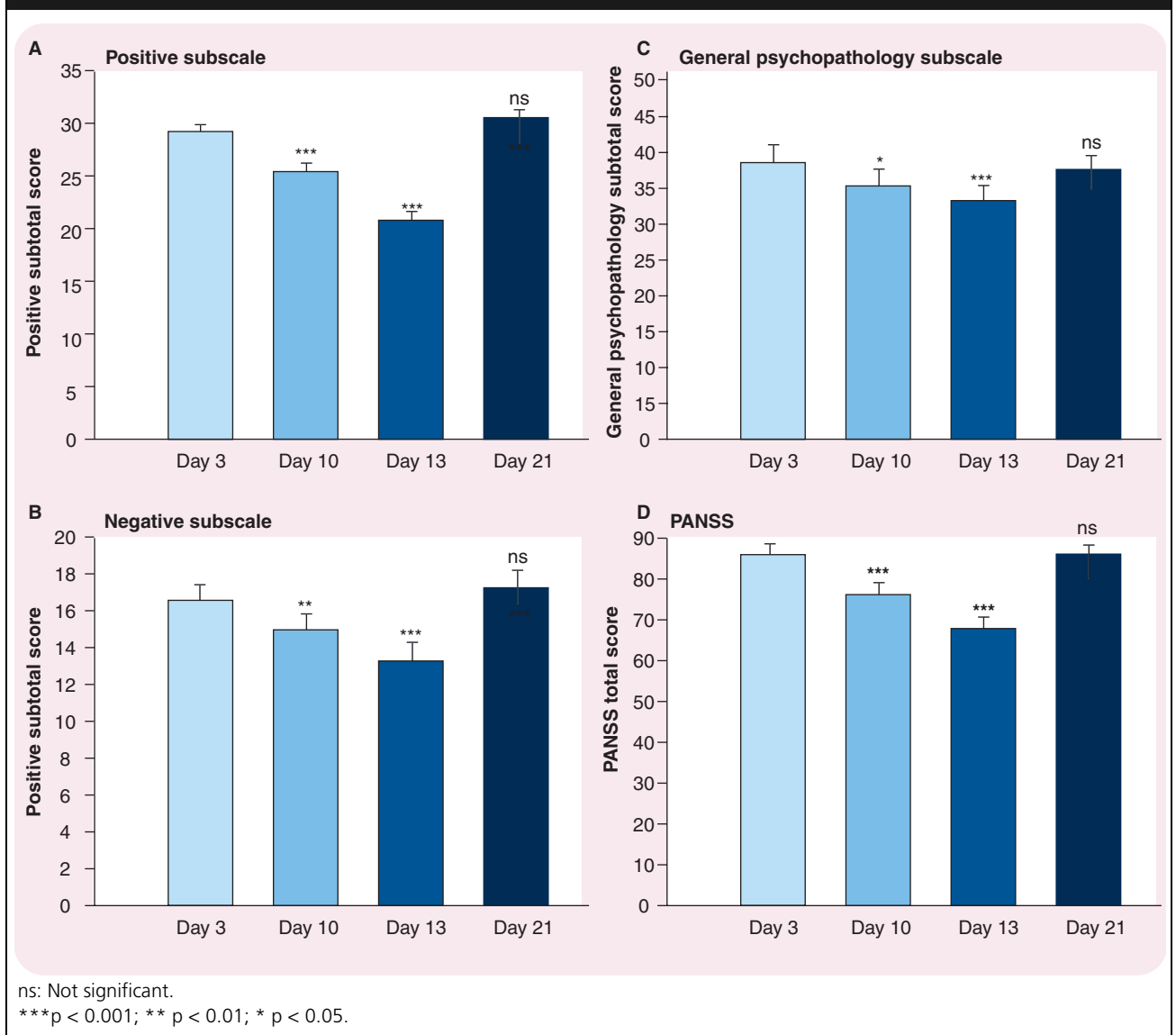
consistent with the findings that psychotic symptoms are exacerbated premenstrually in schizophrenic women [16,17]. In addition, Hoff and colleagues reported that higher estrogen levels in female patients with schizophrenia are associated with better cognitive ability [18]. It has been suggested that estrogen supplementation can augment the treatment effects of antipsychotic drugs [19–21]. Therefore, the present study and reported trials may open a new window in the treatment of schizophrenia. High progesterone level also was associated with better outcome in the present study. There have also been reports concerning serum progesterone levels in the premenstrual phase of women with premenstrual syndrome. This is in line with our finding of low serum progesterone levels in our patients during the premenstrual phase [22,23]. In this study, we found that our patients had low levels of estrogen compared with ranges seen in healthy women [14]. Indeed, antipsychotic medications increase prolactin levels and, presumably, reduce estrogen levels. Therefore, further studies should examine the relationship of prolactin levels to estrogen levels as a means of assessing possible medication effects. Research should also be performed to determine the best mode of hormone replacement for psychiatric patients. In addition, the risk of endometrial cancer and, possibly, breast cancer and coronary heart disease should be considered when using estrogen therapy.

The most important limitation of this study is that all patients had been taking risperidone for at least 4 weeks and their dosages were fixed at 6 mg/day. As a result of this, their psychotic symptoms may have been prevented by risperidone. Despite the limitations of this study, the findings suggest that premenstrual exacerbation of symptoms in female with schizophrenia may be related to low estrogen

Table 2. Comparison of PANSS total scores and its subscales with estrogen and progesterone serum level on day 3 and 13 of the menstrual cycle.

| Comparisons | Day 3 (Mean ± SEM) | Day 13 (Mean ± SEM) | p |
|----------------------------------|-----------------------|------------------------|-----------|
| Positive subtotal | 29.16 ± 0.63 | 20.76 ± 0.83 | p < 0.001 |
| Negative subtotal | 16.4 ± 0.86 | 13.16 ± 1.00 | p < 0.001 |
| General psychopathology subtotal | 38.7 ± 2.31 | 33.13 ± 2.23 | p < 0.001 |
| PANSS total | 84.6 ± 2.64 | 67.23 ± 2.78 | p < 0.001 |
| Estrogen serum level | 51.66 ± 4.87 (pg/ml) | 134.26 ± 3.43 (pg/ml) | p < 0.001 |
| Progesterone serum level | 1.36 ± 00.09 (ng/ml) | 7.63 ± 0.62 (ng/ml) | p < 0.001 |

Figure 4. Changes of mean positive (A), negative (B) and general psychopathology (C) subtotal scores and mean of PANSS total scores (D) over the four stages of the menstrual cycle (days 3, 10, 13 and 21) of all 30 patients with chronic schizophrenia.



level. Many clinicians at this phase tend to increase the dose of antipsychotic medication. Nevertheless, in the premenstrual phase, the aggravated symptoms are not alleviated by merely increasing the dose of antipsychotic medication in some patients. Therefore, various approaches should be considered before increasing the dose.

Conclusion

Although more systematic research is needed to understand the etiology of the sex difference in schizophrenia, the present data add to a growing body of research suggesting that

estrogen has an important role in the brain and higher estrogen levels in the female patients with schizophrenia may be associated with better outcome. Moreover, exacerbation of symptoms during premenstrual period supports the role of reproductive hormones in schizophrenia.

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Highlights

- Sex differences in terms of age at onset, symptom expression, and course of illness have been consistently demonstrated in patients with schizophrenia.
- Recently there have been several reports of a close relationship between estrogen level and severity of psychotic symptoms in schizophrenia.
- Higher estrogen levels are associated with lower severity of symptoms of schizophrenia according to Positive and Negative Syndrome Scale (PANSS).
- Estrogen has an important role in the brain and higher estrogen levels in female patients with schizophrenia may be associated with better outcomes.

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