Relationship Between Gonadal Hormone Levels and Symptom Severity in Female Patients With Schizophrenia

ABSTRACT

Objective: It is thought that sex-specific differences in schizophrenia may be associated with gonadal hormones, especially estrogen. This study aimed to investigate the relationship between follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol, and progesterone serum levels and symptom severity during the menstrual cycle in female patients with schizophrenia.

Methods: Serum samples were taken in the follicular and periovulatory phases from 32 female patients with schizophrenia; and FSH, LH, prolactin, estradiol, and progesterone levels were performed. Simultaneously, the patients were administered positive and negative symptom scale (PANSS), Calgary depression scale for schizophrenia (CDSS), and Hamilton anxiety rating scale (HAM-A).

Results: PANSS ($z = -2.52$, $P < .001$), HAM-A ($z = -3.60$, $P < .001$), and CDSS ($z = -2.52$, $P = .012$) scores were lower in the periovulatory phase than in the follicular phase. Negative correlations between FSH and PANSS positive symptom subscale ($r = -0.393$, $P = .035$), and between prolactin and PANSS total score ($r = -0.406$, $P = .029$) were detected.

Conclusion: Hypoestrogenism should be studied more in patients with schizophrenia. Studies with large samples evaluating FSH, LH, prolactin, and progesterone together with estrogen are needed to be able to safely use gonadal hormones, which may be related to schizophrenia symptom severity, especially in patients who do not respond adequately to treatment.

Keywords: Schizophrenia, sex, estrogen, progesterone, follicle stimulating hormone, luteinizing hormone

Introduction

Sex differences in schizophrenia have attracted the attention of researchers, and there have been various studies dedicated to it in the literature. The age at onset of schizophrenia in men is on an average between 18-24 years; however, it occurs about 4 years posteriorly in females.[1] Nevertheless, a second peak in terms of age of onset in the age range of 45-50 is observed only in females.[2] In 2 independent meta-analyses conducted by excluding confounding factors related to the prevalence of schizophrenia, it was shown that the prevalence is higher (ratio: 1.4/1) in men.[3,4] In addition, it is known that the severity of the disease in schizophrenia is lower in female patients than in male patients, regardless of culture.[5-7] In female patients diagnosed with schizophrenia, positive mood symptom severity are higher than in men, and the severity of negative symptoms are seen to be lower.[8] It has been shown that in women, late onset and mood symptoms are related with good prognosis, whereas in men, early onset and negative symptoms are associated with a poor prognosis.[9] Female patients diagnosed with schizophrenia respond better to antipsychotic treatment than men.[10] In female patients with schizophrenia, quality of life, marriage, and working rates are higher; and in general, they show a better clinical course.[5]

As a result of extensive investigation of sex-specific differences in schizophrenia, the view that gonadal steroids, especially estradiol, are strongly related with its appearance has gained importance.[11] The estrogen hypothesis in schizophrenia suggests that estrogen has a protective effect in women against the development and severity of psychosis.[12,13] Increased symptom severity, higher recurrence rates, and more hospital admissions with low estradiol levels as

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early follicular phase of the menstrual cycle, postpartum, and post menopause period, and the fact that the frequency of schizophrenia makes the second peak in the post-menopausal period with estrogen withdrawal supports the assumption that estrogen has an effect in schizophrenia as mentioned in case reports and clinical studies to date.[14] It is shown that female patients with schizophrenia generally have lower estrogen levels, and menstrual irregularities are more common in this patients.[15,16] It is also known that some antipsychotics used to treat schizophrenia cause hyperprolactinemia, which lowers estrogen levels.[17] Estrogen is thought to have a regulatory effect on the dopaminergic system by its action on dopamine receptors in the central nervous system.[18-20] The estrogen hypothesis draws attention to the protective effect of estrogen by making the second peak of the frequency at the end of the age of 40s, with the withdrawal of estrogen around the late onset and menopause age in female patients,[21] whereas less emphasis has been placed on the role of the other female gonadal hormone, progesterone, whose levels fluctuate throughout the menstrual cycle such as estrogen, and the follicle stimulating hormone (FSH) and luteinizing hormone (LH), which are pituitary hormones that regulate their release.[22]

This study aimed to investigate the changes in FSH, LH, prolactin, estradiol, and progesterone levels throughout the menstrual cycle, assuming that they will affect clinical severity in women diagnosed with schizophrenia and the correlation between the change in serum levels of these hormones and symptom severity throughout the menstrual cycle.

Methods

Participants
The sample included women diagnosed with schizophrenia who were followed up by Eskişehir Osmangazi University School of Medicine psychiatric outpatient clinic between January 2017 and April 2018. The patients and their relatives who agreed to participate in the study were informed, and their consents were obtained. Being a woman over the age of 18 and having a diagnosis of schizophrenia with evaluation of Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) were the inclusion criteria; whereas going through post menopause, irregular menstrual cycle, a diagnosis of mental retardation, presence of a psychiatric disorder other than schizophrenia, and having an endocrine disease which affects the menstrual cycle were defined as exclusion criteria.

Of the 72 female patients over the age of 18 who stated that they had regular menstruation, 24 did not agree to participate in the study, and 1 of them stated that she has a diagnosis of hypophysis adenoma. Although 6 patients agreed to participate in the study and stated that they would reapply again during their menstrual period,

MAIN POINTS
- *The estradiol levels of patients with schizophrenia were detected to be lower compared with the current reference ranges.*
- *Lower PANSS, HAM-A and CDSS scores were found during the mid-luteal period compared with the early follicular phase in patients with schizophrenia.*
- *The negative correlation between the prolactin level and the total PANSS score may be an indirect indicator of the effectiveness of the antipsychotic treatment.*

they could not be reached; 5 patients were excluded from the study owing to the detection of additional mental disorders other than schizophrenia; and 3 patients were not included because of having an additional diagnosis of mental retardation. Another patient was excluded from the study as she did not come to the second measurement period. The remaining 32 female patients, who met the inclusion criteria, were included in our study.

Procedure
Blood samples were taken from the patients who were included in the study in the follicular phase of the menstrual cycle (0-3 days) and in the periovulatory phase (12-14 days) between 09:30 and 11:00 am and the levels of estradiol, progesterone, FSH, LH, and prolactin were examined in Eskişehir Osmangazi University School of Medicine, department of medical pharmacology. The blood samples taken from the patients and contained in the biochemistry tube were centrifuged at 3,000 rpm for 10 minutes. The separated serum was then placed in covered plastic tubes and stored at -20°C until analysis. After serum samples were collected from all the volunteers participating in the study, the preserved serum samples were thawed immediately prior to analysis; and estradiol, progesterone, FSH, LH, and prolactin levels were studied according to the manufacturer's instructions using commercial enzyme-linked immunosorbent assay (ELISA) kits. Calgary depression scale for schizophrenia (CDSS), the positive and negative syndrome scale (PANSS), and the Hamilton anxiety scale (HAM-A) were performed by a blinded researcher simultaneously with the measurement of hormone levels by taking blood samples in the early follicular phase (0-3 days) and periovulatory phase (12-14 days).

Instruments
Sociodemographic Data Form: It is a semi-structured scale developed to record information regarding to sociodemographic and clinical features.

Structured Clinical Interview for DSM-IV Axis I Disorders: It is a diagnostic scale developed by First et al[23] translated into Turkish by Özkürkçügil et al,[24] and a validity and reliability study was conducted.

Calgary Depression Scale for Schizophrenia: It was developed by Addington et al[25] because other depression rating scales could not adequately measure depressive signs and symptoms in patients with schizophrenia. The validity and reliability of the Turkish version of the scale was done by Oksay et al.[26]

Positive and Negative Syndrome Scale: It is a 30-item, 7-point semi-structured interview scale developed by Kay et al,[27] which includes the evaluation of the severity of symptoms in patients with schizophrenia. Of the 30 psychiatric parameters, 7 belong to the positive symptoms subscale, 7 to the negative symptoms subscale, and the remaining 16 to the general psychopathology subscale. The Turkish validity and reliability of the scale was done by Kostakoglu et al.[28]

Hamilton Anxiety Rating Scale: It is a scale used to determine the level of anxiety in the last 72 hours.[29] It is applied to determine the level of anxiety and symptom distribution of the participants and to measure the change in severity. It includes 14 questions evaluated between the scale of 0 and 4. The Turkish translation and validity reliability study was conducted by Yazici et al.[30]

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Statistical Analysis

The Shapiro Wilk's test was used to investigate the compatibility of the data for normal distribution. The 2-way repeated measures analysis of variance (1 factor repeated) test was used for repeated measures. Spearman's correlation analysis was applied to determine the direction and size of the relation between variables. Correction was made according to hormone values in the evaluation of changes in scale scores at different measurement times. SPSS version 21.0 (IBM Corp.; Armonk, NY, USA) software program was used in the application of analyses. A value of *P* < .05 was accepted as a criterion for statistical significance.

The study was approved by Eskişehir Osmangazi University Ethics Committee dated 21/09/2016, #24. This study was supported by the scientific research projects fund of Eskişehir Osmangazi University, project #2016-1341 and dated 25/11/2016.

Results

The sociodemographic information and types of antipsychotic treatments of female patients diagnosed with schizophrenia participating in the study are shown in Table 1.

The mean FSH, LH, prolactin, estradiol, and progesterone levels of the participants in the follicular and periovulatory phase are shown in Table 2.

Table 1. Sociodemographic Characteristics of the Participants

	Mean (SD) (n=32)
Age (years)	35.46 (8.26)
Duration of education (years)	9.31 (4.13)
First psychotic period age	24.81 (8.32)
Age of menarche	13.21 (1.31)
Menstrual cycle duration (days)	29.21 (3.10)
Number of hospitalizations	2.74 (2.75)
	n (%)
Marital status	
Single	23 (72.9)
Married	9 (28.1)
Lives with	
Husband	2 (6.3)
Husband and children	6 (18.8)
Parents	19 (59.4)
Relatives	5 (15.6)
Habitation	
City	26 (81.2)
Country	6 (18.8)
Occupation	
Employed	4 (12.5)
Unemployed	28 (87.5)
Physical disease	
Present	11 (34.4)
Absent	21 (65.6)
Medication	
Single atypical AP	13 (40.6)
Multiple atypical APs	15 (46.9)
Atypical + typical APs	4 (12.5)

Abbreviation: AP, antipsychotic.

The participants' mean PANSS total and positive symptoms, negative symptoms, and general psychopathology subscale scores were significantly lower in the periovulatory phase than in the follicular phase (z = -2.52, *P* < .001; z = -3.60, *P* = .001; z = -3.86, *P* < .001; z = -2.87, *P* = .004, respectively). The participants' mean HAM-A total and psychic symptoms, somatic symptoms subscale scores were significantly lower in the periovulatory phase than in the follicular phase (z = -3.60, *P* < .001; z = -2.78, *P* = .005; z = -2.17, *P* = .029, respectively). The participants' mean CDSS score was significantly lower in the periovulatory phase than in the follicular phase (z = -2.52, *P* = .012) (Table 3).

When the correlation between the changes in FSH, LH, prolactin, estradiol, and progesterone levels during the menstrual cycle of the participants and the change in PANSS, HAM-A, CDSS scores were evaluated, a negative correlation between FSH and PANSS positive symptom subscale (r = -0.393, *P* = .035), and a negative correlation between prolactin and PANSS total score (r = -0.406, *P* = .029) were found (Table 4).

Discussion

The mean age of the participants at first menstruation was 13.21 (SD = 1.31) years in our study. The onset of puberty may be delayed because of low estrogen levels in female patients with schizophrenia.[16] Riecher-Rössler et al[31] have found that indicators of estrogen deficiency such as menarche delay, intermenstrual bleeding, hypomenorrhea, hair loss, and hirsutism were significantly higher in patients with schizophrenia. A relationship was also found between the late age at menarche, more severe negative symptoms and functional impairment in women diagnosed with schizophrenia. This suggests that puberty, which begins at an earlier age will be associ-

Table 2. Hormone Levels of the Participants in the Follicular Phase and the Periovulatory Phase

	Follicular phase Mean (SD) (n=32)	Periovulatory phase Mean (SD) (n=32)
FSH (ng/mL)	13.75 (18.81)	12.29 (15.58)
LH (mIU/mL)	6.46 (5.51)	12.05 (11.44)
PRL (ng/mL)	54.61 (40.29)	52.10 (33.45)
Est (pg/mL)	25.16 (9.70)	59.83 (36.87)
PGN (ng/mL)	2.67 (1.50)	2.82 (1.56)

Abbreviations: FSH, follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; Est, estradiol; PGN, progesterone.

Table 3. Comparison of the Participants' Mean PANSS, HAM-A, and CDSS Scores in Follicular and Periovulatory Phase

	Follicular phase Mean (SD)	Periovulatory phase Mean (SD)	z	*P*
PANSS total	67.34 (21.97)	58.94 (18.70)	-2.52	< .001
Positive	13.56 (5.52)	11.62 (4.17)	-3.60	.001
Negative	20.16 (7.92)	17.47 (7.18)	-3.86	< .001
General	33.88 (10.41)	30.68 (9.39)	-2.87	.004
HAM-A total	12.28 (7.30)	9.43 (6.66)	-3.60	< .001
Psychic	6.38 (3.56)	5.09 (3.18)	-2.78	.005
Somatic	5.90 (4.53)	4.34 (4.05)	-2.17	.029
CDSS	5.97 (4.17)	4.28 (3.62)	-2.52	.012

Abbreviations: PANSS, Positive and Negative Syndrome Scale; HAM-A, Hamilton Anxiety Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; SD, standard deviation.

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Table 4. The Relationship Between Changes in Serum FSH, LH, PRL, Estradiol Levels and Changes in PANSS, HAM-A, CDSS Scores

	FSH		LH		PRL		Estradiol		PGN	
	r	P	r	P	r	P	r	P	r	P
PANSS total	-0.230	.229	0.100	.607	-0.406	.029	-0.123	.524	0.177	.358
Positive	-0.393	.035	0.076	.697	-0.308	.104	-0.257	.179	-0.176	.361
Negative	-0.293	.123	-0.020	.917	-0.332	.079	0.141	.467	-0.214	.265
General	-0.230	.229	0.121	.532	-0.326	.084	-0.137	.478	-0.197	.307
HAM-A total	-0.055	.778	-0.152	.432	-0.219	.254	-0.012	.952	-0.297	.118
Psychic	-0.025	.897	0.041	.832	-0.101	.601	0.022	.909	-0.352	.061
Somatic	-0.011	.955	-0.258	.176	-0.253	.186	-0.053	.785	-0.133	.491
CDSS	0.138	.475	-0.162	.401	-0.304	.109	0.069	.723	-0.039	.839

Abbreviations: PANSS, Positive and Negative Syndrome Scale; HAM-A, Hamilton Anxiety Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; FSH, follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; PGN, progesterone.

ated with a better clinical course.[32] Similarly, an inverse relation was found between the age of menarche and the age of first psychotic symptoms and initial hospitalization.[33] In a study in which they investigated whether there was a difference in the age of menarche between female patients with schizophrenia and mentally healthy women, Kilicaslan et al[34] have found the menarche age of patients with schizophrenia to be 13.53 (SD = 1.36) years and the matched healthy control group to be 13.19 (SD = 1.44) years and evaluated the difference as significant. In another study in which Tekgül et al[35] evaluated 121,449 women between the ages of 15-49 years, they found the mean age of menarche was 13.3 (SD = 1.3) in the general population. Although the absence of a matched healthy control group in our study prevented us from making an adequate evaluation, the mean age of menarche of the participants as 13.21 (SD = 1.31) was found to be similar to the mean age of menarche seen in the general population in our country.

Estradiol levels of the participants in our study were 25.16 (SD = 9.70) pg/mL in the follicular phase and 59.83 (SD = 36.87) pg/mL in the periovulatory phase. The normal reference ranges of estradiol are 25-100 pg/mL for the follicular phase, 150-450 pg/mL for the periovulatory phase, and 70-220 pg/mL for the post-ovulation phase.[16] Although the sample of the study included women who had regular menstruation, the estradiol levels of our participants were detected to be lower compared with the current reference ranges.[36] The low estradiol level in our sample may be related to hyperprolactinemia, which develops owing to the use of antipsychotics. Hyperprolactinemia leads to a decrease in estrogen levels,[17] which could cause a predisposition to menstrual irregularities.[12,16] However, in some recent studies, it was found that serum estrogen levels were generally low throughout the entire menstrual cycle in women with a diagnosis of schizophrenia with regular menstruation,[15] and it was suggested that women with schizophrenia have low estrogen levels independent of irregularities in hormone levels associated with antipsychotic use.[13] Although our findings support a decrease in estrogen levels in schizophrenia, studies comparing drug naive patients with healthy control groups are needed to reveal whether dysfunction of estrogen occurs before or after the onset of schizophrenia.

Despite the improvement detected by scale scores in the periovulatory phase, no significant relation was found between the change in PANSS, HAM-A, and CDSS scores and the change in serum estradiol levels. In schizophrenia, the estrogen hypothesis is supported by late onset age in women, the second peak of frequency with the withdrawal of estrogen around the age of menopause, and

the exacerbation of symptoms in the lower estrogen phases of the menstrual cycle.[21] Bergemann et al[37] have evaluated the severity of clinical symptoms 3 times during the menstrual cycle in 125 premenopausal women diagnosed with schizophrenia and found a significant improvement in psychotic symptoms in the luteal phase correlated with estradiol plasma levels. Riecher-Rössler et al[12] have observed that the estradiol levels of the participants were significantly lower than the population average, and the clinical symptom severity improved with the increase in the estradiol level in their study with 32 women diagnosed with schizophrenia. In a study conducted in our country, a relation was also observed between the decrease of estradiol levels and clinical severity.[38] These findings may be related to estradiol's regulation of the number and sensitivity of dopamine receptors shown by experimental animal studies.[20] Similar to our findings, Rubin et al[39] reported lower total, general, and positive PANSS scores in patients with schizophrenia during the mid-luteal period compared with the early follicular phase. However, no significant relation was found between serum estradiol or progesterone levels and changes in symptoms related to the menstrual cycle.

In our study, a negative correlation was found between the change in prolactin values and the change in the PANSS total score. Since antipsychotic treatment often causes hyperprolactinemia, measuring prolactin levels in drug naïve patients with schizophrenia may be a useful method to assess the association of prolactin to schizophrenia. However, studies conducted till date have revealed different results. Although some studies revealed a significant increase in prolactin levels in patients with newly diagnosed first-episode psychosis compared with healthy controls,[31,40,41] others found the prolactin level to be lower than or equal to the control group.[42,43] The findings on this issue are still controversial. As the increase in prolactin levels is correlated with the D_2 receptor blockade, prolactin may be a useful marker of the resulting blockade and, indirectly, the effectiveness of antipsychotic drugs. A study conducted by Kitamura et al[44] in 96 patients diagnosed with schizophrenia who received fluphenazine decanoate treatment for at least 12 weeks, have found that a higher prolactin/plasma fluphenazine ratio was associated with better clinical results. Otani et al[45] demonstrated the relationship between improvement in positive symptoms and increased plasma prolactin levels in male patients. The negative correlation between the prolactin level and the total PANSS score we found in our study may be an indirect indicator of the effectiveness of the antipsychotic treatment, consistent with the dopamine hypothesis of schizophrenia.

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In our study, there was a negative correlation between the change in FSH levels and the change in the PANSS positive symptoms subscale score. No relation was found in a study evaluating the relation between clinical improvement and FSH/LH ratio.[46] The second peak of the lifetime prevalence of schizophrenia by age observed in menopausal female patients demonstrates that there is a need for further studies on the hormones related to the hypothalamo-pituitary-gonadal axis to determine their relationship with each other and their clinical effects. No significant relation was found between the changes in LH levels and the changes in PANSS, HAM-A, and CDSS scores in our study. During the menstrual cycle, the LH level peaks approximately 16 hours before ovulation, with a 6- to 10-fold increase, and its serum level drops again after ovulation.[47] It is difficult to catch this period in the periovulatory phase, and it limits the evaluation of the clinical effects of LH.

Studies investigating the association between the varying levels of gonadal hormones and schizophrenia symptoms are associated with estradiol; however, very few studies concentrate on the simultaneous fluctuations in progesterone.[22] In general, the improvement in schizophrenia symptoms seen in the mid-luteal phase of the menstrual cycle was attributed to the protective efficacy of estrogen despite the absence of simultaneous serum measurements in these studies.[48] Yet, this mid-luteal phase is a period in which progesterone, like estrogen, is higher than the other phases.[47] Progesterone is also the metabolic precursor of sex steroids such as estrogen and testosterone, as well as glucocorticoids and mineralocorticoids.[47] Therefore, progesterone may have an important role, either directly or indirectly, in schizophrenia. In 1 of the few studies performed, Hoff et al[49] evaluated serum progesterone levels and symptom severity for 4 consecutive weeks in 22 female patients and could not propound a correlation between mean progesterone levels and symptom severity. Nevertheless, it was not reported in which stage of the menstrual cycle the women were when serum samples were taken in this study. Ko et al[50] conducted a randomized controlled study to investigate the effectiveness of 8 weeks supplemental hormone replacement treatment, using estradiol and a synthetic progestin, medroxyprogesterone acetate, in 14 patients with schizophrenia. Hormone replacement treatment was shown to significantly improve negative and cognitive symptoms compared with the placebo in this study. In our study, there was no significant relation between the change in progesterone levels in the follicular phase and the periovulatory phase and the change in PANSS, HAM-A, and CDSS scores. The fact that serum level of progesterone was not evaluated in the mid-luteal phase, when progesterone peaks during the menstrual cycle and similar levels of progesterone in the follicular phase and the periovulatory phase, may be related to the lack of correlation between progesterone levels and scale scores in this study.

The most important limitation of our study was that we had a small sample group of 32 patients, and the patients were under antipsychotic treatment. The absence of a control group in our study meant that we could not evaluate menarche age and hormone levels by comparing them with a matched control group. In our study, hormone level measurements and evaluation with simultaneous scales were performed in the follicular phase and the periovulatory phase. This influenced our full evaluation of the effect of hormones such as progesterone, which peaked in the mid-luteal phase of the menstrual cycle, on scale scores.

One of the important findings of our study, that is the lower levels of estrogen that we detected in women with schizophrenia, is an issue that needs more attention and investigation. Nevertheless, the current literature on hormone levels that may be associated with symptom severity of schizophrenia in women focuses more on estrogen, and it is noteworthy that the presence or role of other hormones such as progesterone, FSH, LH, and prolactin, which are related to the menstrual cycle and at the same time, affect estrogen levels, have not been sufficiently investigated. In schizophrenia, the etiology of which is not yet clear, the inability to achieve complete well-being in some patients with existing treatments may mean we need to look at alternative treatments, such as estrogen augmentation therapy. Further studies which include estrogen along with other gonadal hormones and other related hormones are needed on this subject.

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