Psychiatria Danubina, 2018; Vol. 30, Suppl. 4, pp S175-179 *Conference paper*

INFLUENCE OF HORMONAL STATUS AND MENSTRUAL CYCLE PHASE ON PSYCHOPATOLOGY IN ACUTE ADMITTED PATIENTS WITH SCHIZOPHRENIA

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SUMMARY

Background: *The gender differences in onset, symptom severity, and outcome of schizophrenia are now thought to support the hypothesis that sex hormones may also have a role in etiology, as well as treatment, of schizophrenia. A number of reproductive hormones may be implicated, including testosterone, progesterone, or luteinising hormone, and thus it is important to acknowledge that there is a complex interplay of hormones occurring. This study was introduced to highlight the effect of the menstrual cycle, and sex hormones on female patients with schizophrenia.*

Subjects and methods: *The sample consisted of 31 consecutively acute admitted women, aged 18 to 45 years with schizophrenia diagnosed by DSM-5 criteria. The sample consisted of women who were regulary menstruating and to be undergoing regular hormonal fluxes. Each subject was enrolled and received psychopathology and hormone (estradiole, progesterone, testosterone) assessments. Psychopathology was measured with Positive end Negative Syndrome Scale (PANSS). The subjects were divided into folicular (high estrogen) and luteal (low estrogen) phase admissions. Data were analyzed by regression analysis and t-test for independent samples. Values are given as means ±SD.*

Results: *There were no differences between the folicular and luteal phase admission grups with regard to age, duration of illness and age at onset of illness. We found that significantly more women were admitted during the luteal (low estrogen) phase of menstrual cycle (68%) as compared to follicular (high estrogen) phase (32%).*

Conclusion: *There was a significant increase in hospital admissions in the luteal phase of menstrual cycle in women suffering from exacerbation of schizophrenia. The influence of particulary sex hormones (estrogen, progesterone and testosterone) on admission rate and clinical psychopatology was found insignificant.*

Key words: *schizophrenia – women - hormonal status - psychopathology*

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INTRODUCTION

Hormone research in women with schizophrenia is still in its infancy. Many women with schizophrenia describe subjective observations of correlations between changes in menstrual cycle and the onset or relapse in psychotic symptoms (Seeman 1996, Harris 1997, Kulkarni 2015). Gender differences in onset, symptom severity, and outcome of schizophrenia are now thought to support the hypothesis that sex hormones may also have a role in the etiology, as well as treatment, of schizophrenia (Fink et al. 1996, Gogos et al. 2015).

Research over the last two decades has established a clear neuromodulatory role of estrogen in the pathogenesis and therapeutics of neuropsychiatric disorders including schizophrenia (Sayed et al. 2003). It has been reported in many studies that estrogen has a significant impact on the psychological state of women. It is known that schizophrenia initiates in the older age and shows a better clinical course in women than in men (Lindamer & Lohr 1991, Kılıçaslan et al. 2014). It is thought that estrogen is protective against schizophrenia with its antidopaminergic effect (Riecher-Rossler & Hafner 1993, Castle et al. 1995). Furthermore, seeing a second peak in the prevalence of schizophrenia during the postmenopausal period in women could be evidence of the protective effect of estrogen against schizophrenia. Moreover, it is known that lower doses of antipsychotic treatment are sufficient in female patients than in male patients with schizophrenia and that antipsychotic doses may need to be increased during the postmenopausal period in women (Kolakowska & Williams 1985, Guz 2000). It was shown that there is a negative relation between blood estradiol levels and negative findings of schizophrenia and that schizophrenia finding intensity decreases as estradiol levels increase (Seeman & Lang 1990, Hallonquist et al. 1993). It was shown that in female patients with schizophrenia the intensity of the disease is changeable during the menstrual cycle and that deterioration is likely to be during low estrogen phases. The intensity of the disease usually reduces during pregnancy. However, recurrences are usually observed during the postpartum period (Grigoriadis & Seeman 2002, Huber et al. 2004). The most common interpretation of these gender differences is the well-described "estrogen hypothesis," which postulates that estrogen plays a protective role against schizophrenia (Hafner et al. 1998, Seeman 2012).

However, it is important to note that studies describing gender differences in schizophrenia suggest sex steroid dysfunction, not necessarily only estrogen dysfunction. A number of reproductive hormones may be implicated, including testosterone, progesterone, or luteinising hormone, and thus it is important to acknow-

ledge that there is a complex interplay of hormones occurring. For example, progesterone and estrogen naturally vary with each other over endogenous hormonal cycles; therefore the influence of progesterone or an interaction between the two hormones on the observed phenomena cannot be excluded (Wieck 2011, Hayes et al. 2012, Kulkarini et al. 2012). While there has been significant attention placed on the impact of estrogens in schizophrenia, less consideration has been afforded to the role of progesterone, the other main female gonadal hormone. Literature discusses the role of progesterone as a neuroactive steroid and that it may be dysregulated in schizophrenia. Preclinical and molecular studies relevant to schizophrenia are discussed with a particular focus on the interactions between progesterone and the dopaminergic system. Existing data on progesterone in relation to schizophrenia is inconsistent, with some studies suggesting a neuroprotective role for the hormone (e.g. animal models of cognitive dysfunction and positive symptoms), while other studies posit a disruptive impact of the hormone (e.g. negative correlations with symptom modulation in patients) (Sun at al. 2016). Progesterone and related steroids are thought to exert a sedative effect (Sun et al. 2016). Estrogene induced brain progesterone receptors; hance, the action of estrogen could also be partly mediated by progesterone. Estrogen may potentiate the sedative action of progesterone by stimulating an increase in progesterone receptors during the luteal phase of the menstrual cycle and during pregnancy. The drop in plasma progesterone concentrations at the end of the luteal phase may account for anxiety symptoms in women with premenstrual syndrome (Fink et al. 1996). A longitudinal, as well as cross-sectional, view of the hormonal and clinical data suggests that the testosterone system is linked to both state and trait psychological factors (Mason at al. 1988, Misiak et al. 2018).

SUBJECTS AND METHODS

The sample consisted of 31 consecutively acute admitted women, aged 18 to 45 years (mean age 35.2±6.84 years) with schizophrenia diagnosed by DSM-5 criteria. The mean duration of the illness was 10.90±6.11 years. All patients were acutely admitted to acute ward for female psychotic disorders et the University Psychiatric Hospital Vrapče in Zagreb. The sample consisted of women who were regulary menstruating and to be undergoing regular hormonal fluxes. Observed menstrual cycle lenght varied from 21 to 45 days, with an average of 29.6 days. Women with an irregular menstrual cycle or without exact statments on the time of their last menstruation were not included in the study. Women were excluded if they were taking any synthetic steroids including the oral contraceptive, if they were pregnant, lactating or postmenopausal. All patients gave written informed consent, and the University Psychiatric Hospital Vrapče Ethics Committee approved the study. Each subject was enrolled and received psychopathology and hormone (estradiole, progesterone, testosterone) assessments. Psychopathology was measured with Positive end Negative Syndrome Scale (PANSS). Evaluation of clinical status and PANSS was done by an experienced psychiatrist blind with regard to the menstrual phase et admission. Hormone assays for serum estrogene, progesterone and testosterone were performed. The subjects were divided into folicular (high estrogen) and luteal (low estrogen) phase admissions. Folicular and luteal phases were anchored to individual menstrual flow onset. The luetal phase was defined as period of 14 days before first day of menstruating. Data were analyzed by regression analysis and t-test for independent samples. Values are given as means ±SD. This study was introduced to highlight the effect of the menstrual cycle, and sex hormones on female patients with schizophrenia.

RESULTS

We demonstrated an estrogen, progesterone and testosterone effects and affect of phase of menstrual cycle on general psychiatric symptoms and, more specifically, on the positive, negative and general subscore on the Positive and Negative Syndrome Scale (PANSS) on the time of acute psychiatric hospital admission. There were no differences between the folicular and luteal phase admission grups with regard to age, duration of illness and age at onset of illness (Table 1). We found that significantly more women were admitted during the luteal (low estrogen) phase of menstrual cycle (68%) as compared to follicular (high estrogen) phase (32%, p-value=0.0068) (Table 1). We found higher level of progesterone and testosterone in women in luteal phase and higher level of estrogen in folicular phase, but this findings were not statistically significant (Table 2). We did not find any statistically significant differences in psychopatology masured by PANSS scale and PANSS subscale at the time of admission in women with schizophrenia and found no correlations between sex hormones and psychopatology (Table 3, Table 4.1-4).

Table 1. Individual Variables in Women with Schizophrenia Admitted in the Luteal phase and Folicular phase of the Menstrual Cycle

	Luteal phase (n=21)	Folicular phase (n=10)	Total (n=31)	p-value
Age (years)	34.76±6.39	35.5±6.96	35±6.48	0.7716*
Duration of illnes (years)	11.38±5.93	9.9±6.67	10.90±6.11	0.5372*
Age of onset (years)	23.38±5.70	25.6±6.17	24.10±5.84	0.3315*

*unpaired t-test

Table 2. Level of Estrogene, Progesterone and Testosterone in Luteal and Folicular phase

	Luteal phase (n=21)	Folicular phase (n=10)	Total (n=31)	p-value
Estrogene (pmol/L)	300.05±260.07	585.3±634.17	392.06±429.09	0.0834*
Progesterone (nmol/L)	8.61±12.21	3.77±3.21	7.05±10.38	0.2310*
Testosterone (nmol/L)	1.13±0.75	0.98±0.52	1.08±0.68	0.5742*

*unpaired t-test

Table 3. Psychopatology at the Time of Hospital admission in Women with Schizophrenia in the Luteal phase and Folicular phase of the Menstrual Cycle

	Luteal phase (n=21)	Folicular phase (n=10)	Total (n=31)	p-value
PANSS total	96.19±6.66	98±5.94	96.77±6.40	0.4707*
PANSS positive	23.52±2.58	24.2±2.74	23.74±2.61	0.5064*
PANSS negative	21.71±2.50	21.9±1.73	21.77±2.25	0.8305*
PANSS general	50.95±3.49	51.9±3.21	51.26±3.38	0.4736*

*unpaired t-test

Table 4.1. PANSS positive subscale in correlations with hormones

	p-value
Estrogene	0.4239*
Progesterone	0.2406*
Testosterone	0.9860*

* linear regression

Table 4.2. PANSS negative subscale in correlations with hormones

	p-value
Estrogene	0.3659*
Progesterone	0.8638*
Testosterone	0.2557*

* linear regression

Table 4.3. PANSS general subscale in correlations with hormones

	p-value
Estrogene	0.1900*
Progesterone	0.9805*
Testosterone	0.5317*

* linear regression

Table 4.4. PANSS total score in correlations with hormones

	p-value
Estrogene	0.4891*
Progesterone	0.5863*
Testosterone	0.9379*

* linear regression

DISCUSSION

We found that significantly more women with schizophrenia were admitted during the luteal (low estrogen) phase of menstrual cycle (68%) as compared to follicular (high estrogen) phase. This finding has been observed before and applies to all female psychiatric admissions, regardless of diagnosis (Luggin et al. 1984). An early study reported that, of the sample of 276 women admitted to psychiatric hospitals, 46% were admitted during or immediately before menstruation, a period of low circulating estrogen levels (Dalton 1959). Further, psychotic symptoms were reported to improve during pregnancy (Chang & Renshaw 1986), but worsened postpartum (Kendell et al. 1987).

In our study PANSS total score, positive, negative and general subscore were slightly higher in luteal phase group but not significant. In previous studies less severe symptoms correlated with higher estrogen levels. More severe symptoms were associated with lower estrogen levels. More recently, case reports and clinical studies have shown that women with schizophrenia demonstrate increased symptom severity, greater relapse rates, and more hospital admissions during times of low circulating sex hormones, including the early follicular phase of the menstrual cycle, postpartum, and postmenopause (Riecher-Rossler et al. 1994, Bergemann et al. 2002, Bergemann et al. 2005, Rubin et al. 2010). In contrast, rates of relapse are less frequent and symptom severity is reduced during times of high circulating sex hormones, including pregnancy and the mid-luteal stage of the menstrual cycle (Bergemann et al. 2002, Huber et al. 2004). For example, Hallonquist et al. (1993) assessed the variation in symptom severity in female outpatients with schizophrenia during two phases of the menstrual cycle. The authors found that symptom scores as measured by the Abbreviated Symptom Checklist were distinctly low during the mid-luteal phase but high during the early follicular phase. Similarly, Rubin et al. (2010) reported that female patients with chronic schizophrenia showed less severe positive symptoms and general psychopathology (measured using the Positive and Negative Syndrome Scale, PANSS) during the mid-luteal phase versus the early follicular phase, whereas negative symptom severity did not change across the cycle.

We found no statistically significant diffrences in psychopatology measured by PANSS scale and PANSS subscale at the time of admission in women with schizo-

phrenia, and found no correlations between sex hormons and psychopatology in our study. Some studies have specifically shown that there is a negative correlation between circulating estrogen levels and symptoms of schizophrenia, particularly the positive symptoms (Halari et al. 2004, Bergemann et al. 2007). In 125 premenopausal women with schizophrenia, Bergemann and colleagues (2007) assessed psychopathology scores three times during the menstrual cycle. Using the PANSS and Brief Psychiatric Rating Scale, they found a significant improvement in psychotic symptoms during the luteal phase, which was associated with estradiol plasma levels.

The relation between schizophrenia and the menstrual cycle has always been found attractive by researchers. It is accepted that female reproductive hormones regulate the functions of neurotransmitters such as serotonin, dopamine, norepinephrine, and gamma-aminobutyric acid and that hormone fluctuations may lead to mental complaints (Akdeniz & Karadag 2006). It was reported that there could be fluctuations in the psychotic findings of schizophrenic patients during the menstrual cycle and that in the phases where estrogen levels are low, the intensity of the disease may be higher (Riecher-Rossler et al. 1994, Tomruk et al. 2000, Choi et al. 2001). On the other hand, it is still a question of debate whether the clinical picture deteriorates because of hormonal changes during the perimenstrual period or because of the addition of premenstrual syndrome on psychotic findings accompanied by anxiety, depression, and somatic complaints (Seeman 2012).

Increase in estrogen sensitivity in dopaminergic receptors at the luteal phase of the menstrual cycle in schizophrenic patients could account for an increase in psychotic findings (Wieck et al. 2003). Riecher-Rössler et al. (1994) showed that there is a decrease in the severity of positive psychotic findings together with an increase in estrogen levels. Halari et al. (2004) also showed that there is a relation between high estrogen levels and low positive symptom intensity in schizophrenic patients. Bergemann et al. (2002) showed that psychiatric applications were higher during the perimenstrual period when the estrogen levels are low. It is reported in late-initiated female schizophrenic patients, in particular, that estrogen augmentation therapies could be appropriate.

In female patients with schizophrenia, questioning the severity of psychotic findings is of great importance during the menstrual cycle. It may be effective to increase the dose of an antipsychotic that would not increase prolactin secretion 3–5 days before menstruation in patients whose psychotic symptoms intensified. Selective estrogen receptor modulators, which may be effective on estrogen receptors, in the brain, in particular, could be used in psychotic disorders related to the menstrual cycle (Bergemann et al. 2007, Seeman 2012).

Our study has some methodological limitations that require caution in the interpretation of our results. The date of hospital admission does not necessarily reflect the date of the relapse. Many women do experience an aggravation of mood symptoms in the late luteal phase of their cycle, and there is a possibillity that we contaminate the interpretation of our findings. Also, our study included rather small number of patients.

CONCLUSION

Our study showed a significant increase in hospital admissions in the luteal phase of menstrual cycle in women suffering from exacerbation of schizophrenia. The influence of particulary sex hormones (estrogen, progesterone and testosterone) on admission rate and clinical psychopatology was found insignificant. We think that this investigation should be continued on a bigger sample size to highlight the effect of the sex hormones on clinical state and therapy (individual adjustment of antipsycotic doses) in women with schizophrenia.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Miroslav Herceg, Krešimir Puljić and Mirna Sisek Šprem contributed to the data collection.

Miroslav Herceg substantial contributed to conception and design, revision of the results and making conclusions.

Dora Herceg, Mirna Sisek Šprem and Krešimir Puljić contributed to the literature search and revised manuscript for important intellectual content and substantial contributed to conception and design.

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