Plasma concentrations of estradiol in women suffering from schizophrenia treated with conventional versus atypical antipsychotics

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Abstract

\textbf{Background:} Low estrogen levels leading to an elevated rate of menstrual dysfunctions such as amenorrhea and irregular menstruation have been described in women with schizophrenia and have often been attributed to antipsychotic-induced hyperprolactinemia. However, there is some evidence that “hypoestrogenism” in schizophrenic women does not occur exclusively under medication with hyperprolactinemia-inducing antipsychotics. While the precise mechanism of low estrogen levels in schizophrenic women has not been elucidated yet, “hypoestrogenism” is of clinical relevance because estrogen seems to endow an antipsychotic-like effect in schizophrenia and thus positively affect the course of illness in schizophrenic women. In addition, low levels of estrogen might have a negative effect on bone mineral density and on the cardiovascular system.

\textbf{Methods:} To test the “hypoestrogenism hypothesis”, hormone levels in 75 women with schizophrenia diagnosed according to DSM-IV and ICD-10 were determined in the follicular, periovulatory, and luteal phases of the menstrual cycle. Levels of estradiol, prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone, and testosterone were assessed.

\textbf{Results:} The serum levels of estradiol were generally reduced during the entire menstrual cycle compared to normal reference values. With low levels of LH over the entire cycle and of progesterone in the luteal phase, anovulatory cycles were assumed. Hypoestrogenism was found in about 60% of the patients in accordance with a strict definition (estradiol serum level below 30 pg/ml in the follicular phase and below 100 pg/ml in the periovulatory phase). To rule out a possible effect of hyperprolactinemia on the gonadal axis and a subsequent effect on estradiol levels from treatment with conventional (“typical”) antipsychotics, serum estradiol levels of patients treated with certain atypical antipsychotics known to induce only a mild increase in prolactin, or no increase at all, were compared with those from patients treated with conventional...
antipsychotics. The data clearly indicate high prolactin levels in the latter, but low levels in the group treated with atypical antipsychotics. In both groups, however, low levels of estradiol compared to normal reference values were measured.

Conclusions: The present findings provide evidence that hypoestrogenism in schizophrenia occurs in women with and without antipsychotic-induced hyperprolactinemia. Further research should be conducted to clarify the cause of hypoestrogenism in schizophrenic women and focus on possible clinical implications.

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1. Introduction

In addition to the genuinely hormonal functions in the gonadal axis, estrogens also have cerebral effects. Estrogens have been shown to affect major neurotransmitter systems and brain regions responsible for cognitive, emotional, and vegetative functions (e.g., Fink et al., 1996, 1998; Halbreich et al., 1995; Morissette and DiPaolo, 1993; DiPaolo, 1994; Gordon et al., 1980). Furthermore, estrogens exert neurotrophic and neuroprotective effects which are mediated by nongenomic as well as by direct and indirect genomic pathways (for review, see McEwen and Alvers, 1999; Lee and McEwen, 2001; Garcia-Segura et al., 2001; Behl, 2001). The influence of estrogen on the course of various diseases of the nervous system such as stroke, Parkinson’s disease, Alzheimer’s disease, depression, and schizophrenia has been the focus of research in neuroscience over the last two decades. An important starting point of research in these fields was the gender difference in the incidence and recovery from neurological damage and mental disorders.

In schizophrenia research, the estrogen hypothesis has been subject to investigation in the past few years (cf. Bergemann and Riecher-Rössler, 2004). It assumes, in particular, a protective effect of estrogen in women vulnerable to schizophrenia. Evidence for the estrogen protection hypothesis has been derived from animal, epidemiological, and clinical studies.

Kraepelin (1909) was the first to observe that first-time hospitalization in men with schizophrenia occurs earlier than in women (cf. Angermeyer et al., 1988). Häfner et al. (1991, 1992, 1998) showed that a later first-time admission of women was due to a later onset of the disease as compared to men. In addition, and in contrast to men, the curve of age at onset for women shows not only a peak at a young age but also a second smaller peak at the age of 45–49. Supported by these epidemiological data, it seems plausible that between menarche and menopause women have a higher vulnerability threshold to schizophrenia than men because of the protective effect of higher plasma concentrations of estradiol unless genetically determined vulnerability or pre- and perinatal brain injury are taken into account (Albus and Maier, 1995; Könecke et al., 2000).

Cohen et al. (1999) showed an inverse relation between menarche and ages for both the first psychotic symptoms and the first hospitalization in women suffering from schizophrenia; that is, an earlier puberty was a predictor for a later onset of schizophrenia. This finding lends support to the hypothesis that long-lasting effects of estradiol in the brain can raise the vulnerability threshold for psychotic symptoms.

Several clinical studies, often case reports or case series, show a correlation between low estrogen plasma concentrations and an increase in the risk for schizophrenic symptoms in women (cf. Mahé and Dumaine, 2001) as it occurs physiologically postnatally or after the menopause (cf. Seeman, 1997). During pregnancy, when estrogen plasma levels are high (especially the estrogen metabolite estriol), low rates of relapse have been observed in women with schizophrenia (Chang and Renshaw, 1986; Kendell et al., 1987).

Furthermore, there is some evidence for an inverse correlation between the estrogen plasma concentration across the menstrual cycle and psychopathological symptoms in women with schizophrenia (e.g., Riecher-Rössler et al., 1994). Gattaz et al. (1994) showed a significant correlation between the estradiol plasma concentration and the therapeutically required dose of antipsychotics.

Some studies have focused on the correlation between the menstrual cycle phase and the exacerbation of schizophrenic symptoms or hospitalization of acutely ill schizophrenic women, respectively (e.g.,
Bergemann et al., 2002). However, the observation of a possible relationship between phases of the menstrual cycle and psychotic illness dates back many years and was discussed extensively in the nineteenth century (e.g., Häffner, 1912; Mayer, 1872; Ross, 1909; Schroeter, 1874; Krafft-Ebing, 1878; Jolly, 1915; Schaefer, 1894).

Evidence for the estrogen hypothesis can also be derived from studies in which estrogen has been used to treat schizophrenic women, or in which the effect of hormone replacement therapy with estrogen on schizophrenic symptoms has been examined (Kulkarni, 2004; Kulkarni et al., 1996, 2001; Lindamer et al., 2001; cf. Bergemann et al., 2004a).

Although estrogen has been proven to have a protective effect in schizophrenia in numerous investigations, little work has been undertaken to study the estrogen deficiency syndrome or hypoestrogenism hypothesis in schizophrenia, which postulates an association between schizophrenia and a chronic estrogen deficiency not attributed to the medication with antipsychotics—at least in some schizophrenic women (Riecher-Rössler, 2003). The conventional so-called “typical” antipsychotics in particular are known to induce hyperprolactinemia, which in turn suppresses gonadal function (Smith et al., 2002). Low estrogen levels leading to an elevated rate of menstrual dysfunctions such as amenorrhea and irregular menstruation have been described in women with schizophrenia. In this context, particular emphasis should be placed on studies carried out in the pre-antipsychotic era, which demonstrated different types of menstrual cycle disorders in schizophrenic psychoses, anomalies of secondary sexual features, and an increased rate of virilization (e.g., Häffner, 1912; Bleuler, 1943; Reiss, 1958; Diczfalusy and Lauritzen, 1961; for review, see Bergemann et al., 2004b).

More recently, Riecher-Rössler et al. (1994) reported lower than normal estradiol plasma concentrations in the course of the menstrual cycle, with narrow fluctuations in 32 acutely ill premenopausal women with schizophrenia and a history of regular menstrual cycles. Even the narrow fluctuations in the estradiol plasma levels described in this study correlated with psychopathology scores measured by various rating scales.

Furthermore, clinical studies by Choi et al. (2001), Huber et al. (2001), Hoff et al. (2001), and Canuso et al. (2002) provided some evidence for a sex hormone dysregulation and hypoestrogenism in schizophrenia and some indication that hypoestrogenism in schizophrenic women occurs independently of the use of antipsychotics, but data are still sparse.

Therefore, the objective of the present study was to find out whether a larger sample can prove the assumed hypoestrogenism in schizophrenia. For this purpose, the serum levels of 17β-estradiol and other hormones relevant in this context—prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone, and testosterone—were observed during the entire course of the menstrual cycle. Furthermore, we attempted to clarify whether hypoestrogenemia varies depending on the type of antipsychotic the patients received. Most of the time hypoestrogenemia in patients with schizophrenia is attributed to hyperprolactinemia due to conventional antipsychotics via hypothalamic–pituitary feedback mechanisms (Smith et al., 2002; Melkerson et al., 2001). However, it is also known that, in contrast to conventional antipsychotics, some of the newer atypical antipsychotics only cause a minimal or no increase in prolactin levels; low estrogen levels occurring during the treatment with atypical antipsychotics could therefore support the hypothesis of primary hypoestrogenemia in schizophrenia.

2. Methods

2.1. Study design and subjects

In 75 premenopausal, menstruating women with schizophrenia diagnosed according to DSM-IV and ICD-10 and consecutively admitted to the psychiatric unit at the Department of Psychiatry at the University of Heidelberg, hormone levels were assessed three times during the first menstrual cycle after admission to the hospital: at the follicular (proliferative) phase at day 2–4 (t₁), at the periovulatory phase at day 10–12 (t₂), and at the luteal phase at day 20–22 (t₃). The results were compared to normal reference values by the Department of Obstetrics and Gynecology at the University of Heidelberg (Rabe and Runnebaum, 1997; Klinga, 1997).

Patients were included in the study after a diagnosis of schizophrenia was confirmed by a
research psychiatrist using a DSM-IV- and ICD-10-based interview and by review of the patient’s records. In addition, the gynecological history was assessed by a structured interview (adapted from Leidenberger, 1992).

Patients currently being treated with hormone replacement therapy or oral contraceptives were excluded from the study, as were women with amenorrhea or irregular menses for any reason, including malnutrition, stress, and any endocrine or gynecological disease. Women who had undergone surgery affecting gonadal function were also excluded from the study. None of the patients included in the study had been pregnant, given birth, or lactated in the 3 years preceding the study. All patients were receiving some kind of antipsychotic medication, and most of them were also taking other psychotropic substances such as anticholinergic medication, antidepressants, mood stabilizer, benzodiazepines, or a second antipsychotic drug. All patients included in the study reported regular menses.

The patients participating in the study gave their informed consent before inclusion. The study protocol was approved by the local ethics committee at the University of Heidelberg.

All participants were Caucasian. The mean age was 32.9 years, with a standard deviation of 6.8 years (range: 18–46 years). The mean duration of illness was 7.5 ± 7.0 years and the mean number of hospitalizations was 3.8 ± 4.7 (Table 1).

To rule out a possible effect of hyperprolactinemia on the gonadal axis and the subsequent effect on the estrogen level due to the intake of conventional antipsychotics, serum levels of estradiol in women treated with atypical antipsychotics known to induce only a mild or no increase in prolactin were compared to those women treated with conventional antipsychotics. For this additional analysis, subgroups of patients were selected from the entire sample who had been treated continuously for at least 12 weeks with clozapine (n=11) or olanzapine (n=7) and who had received no other medication in this period of treatment. These subgroups were compared to 31 patients treated continuously for at least 12 weeks with one conventional antipsychotic (12 with flupentixol, 4 with perphenazine, and 5 each with haloperidol, perazine, and/or fluphenazine, respectively). The antipsychotic was selected for each patient according to clinical requirements only, without predefining the drug or dose. There was no statistically significant difference between the groups regarding age, duration of illness, and number of hospitalizations (analysis of variance, cf. Table 1).

2.2. Blood specimens and laboratory analysis

Blood specimens were taken between 8 and 9 a.m., i.e., 10–24 h after taking the last oral dose of antipsychotic. Blood levels of 17β-estradiol, prolactin, LH, FSH, progesterone, and testosterone were assessed. For laboratory analysis of all the parameters, an electrochemical luminescence immunoassay was used (Roche Elecsys 2010 immunoassay analyzer).

 Estradiol values of <100 pg/ml during the periovulatory phase (day 10–12 of the menstrual cycle) and <30 pg/ml during the follicular phase (day 2–4) were considered hypooestrogenemic.

The various hormone levels we found were compared to normal reference values of healthy premenopausal women used at the Department of Obstetrics and

<table>
<thead>
<tr>
<th>Sample Subgroups</th>
<th>Clozapine (n=11)</th>
<th>Olanzapine (n=7)</th>
<th>Conventional neuroleptics (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>M±S.D.³</td>
<td>M±S.D.</td>
<td>M±S.D.</td>
</tr>
<tr>
<td></td>
<td>32.9±6.8</td>
<td>32.3±6.7</td>
<td>33.2±8.9</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>M±S.D.</td>
<td>6.4±5.5</td>
<td>11.6±8.7</td>
</tr>
<tr>
<td></td>
<td>7.5±7.0</td>
<td>34.2±6.5</td>
<td>9.6±7.4</td>
</tr>
<tr>
<td>Number of hospitalizations</td>
<td>M±S.D.</td>
<td>4.7±4.2</td>
<td>4.8±5.6</td>
</tr>
</tbody>
</table>

* Analysis of variance.
³ Mean±standard deviation.
Gynecology at the University of Heidelberg (Rabe and Runnebaum, 1997; Klinga, 1997).

2.3. Statistical analysis

Besides standard descriptive statistics, inference statistical procedures were applied. To test for changes over the time of the menstrual cycle, analysis of variance for repeated measurements was performed, with plasma concentration as a dependent variable and menstrual cycle phase as a within-subject factor. To account for the lack of independence, the Huyhn–Feldt correction was applied to the p-values. To test for differences between the subgroups of patients receiving conventional antipsychotics versus clozapine and/or olanzapine regarding age, duration of illness, and number of hospitalizations, analysis of variances was conducted. To test for the difference between the three groups receiving different antipsychotics regarding 17β-estradiol and prolactin, a linear regression analysis with robust standard error was used; the pairs group comparison was conducted in pairs by means of the Wald-test with Sidak correction to compensate for multiple testing. The statistical analyses were calculated with Stata 8 (Stata Corp, 2003).

3. Results

3.1. Course of hormone levels during the menstrual cycle

Hormone levels of 17β-estradiol, prolactin, LH, FSH, progesterone, and testosterone observed during the three phases of the menstrual cycle–days 2–4, 10–12 and 20–22–are listed in Table 2, along with the normal reference values (cf. Rabe and Runnebaum, 1997; Klinga, 1997).

The serum levels of estradiol were generally reduced during the entire menstrual cycle although there were significant changes in the estradiol serum levels between the three phases of the menstrual cycle investigated (p=0.007, analysis of variance for repeated measurements with Huyhn–Feldt correction). According to the normal reference range, one would expect estradiol plasma levels of between 40 pg/ml and a maximum of 100 pg/ml in the follicular phase (cycle day 2–4) and values of above at least 150 and up to 350 pg/ml during the periovulatory phase (cycle day 10–12); in the latter cycle phase, only five patients showed values higher than 150 pg/ml and were thus within the normal range.

The levels of LH were also low throughout the entire cycle. As would be expected, no significant increase in LH could be seen during the periovulatory phase. With a mean progesterone level of 1.56 ng/ml in the luteal phase (cycle day 20–22), it was assumed that ovulation had not occurred and/or that the follicles had not matured sufficiently (normal reference value: >10 ng/ml). As expected, the progesterone levels in the follicular and periovulatory phase of the menstrual cycle were significantly lower (p=0.003).

The prolactin levels were significantly elevated throughout the entire menstrual cycle, as could be expected under medication with predominantly conventional antipsychotics, and no difference between the mean values and deviation between the three phases could be detected.

The mean FSH levels were within the normal range throughout the menstrual cycle, and the mean

<table>
<thead>
<tr>
<th>Day of menstrual cycle</th>
<th>2–4</th>
<th>10–12</th>
<th>20–22</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>17β-Estradiol (pg/ml)</td>
<td>29.9±28.8 (40–300)</td>
<td>52.7±55.7 (150–350)</td>
<td>43.7±50.8 (30–200)</td>
<td>0.007</td>
</tr>
<tr>
<td>Prolactin (mE/l)</td>
<td>1450±1197 (70–410)</td>
<td>1507±1134 (70–410)</td>
<td>1545±1209 (70–410)</td>
<td>0.648</td>
</tr>
<tr>
<td>LH (mE/ml)</td>
<td>3.98±3.03 (1–10)</td>
<td>5.61±7.89 (30–80)</td>
<td>4.54±6.76 (1–10)</td>
<td>0.253</td>
</tr>
<tr>
<td>Progesterone (ng/ml)</td>
<td>0.20±0.17 (0.2–2)</td>
<td>0.36±1.02 (1–2)</td>
<td>1.56±3.10 (&gt;10)</td>
<td>0.003</td>
</tr>
<tr>
<td>FSH (mE/ml)</td>
<td>6.24±3.87 (2–14)</td>
<td>6.67±4.58 (2–14)</td>
<td>5.59±3.71 (2–20)</td>
<td>0.073</td>
</tr>
<tr>
<td>Testosterone (pg/ml)</td>
<td>527±377 (200–600)</td>
<td>577±321 (200–600)</td>
<td>546±330 (200–600)</td>
<td>0.330</td>
</tr>
</tbody>
</table>

p-values refer to the hypothesis of no change in plasma level over the course of the cycle.
testosterone levels were in the upper normal range during all phases of the cycle.

3.2. Hypoestrogenism

In accordance with a strict definition–plasma levels of estradiol of below 30 pg/ml in the follicular phase (cycle day 2–4) and below 100 pg/ml in the periovulatory phase (cycle day 10–12)–we found hypoestrogenism in 57.3% of the patients (95% confidence of interval 45.9–68.8), as shown in Fig. 1.

3.3. Plasma concentrations of estradiol in women with schizophrenia treated with conventional versus atypical antipsychotics

In addition to the description of the hormone levels throughout the menstrual cycle, subgroups of the sample treated continuously over a period of at least 12 weeks with conventional versus atypical (clozapine, olanzapine) antipsychotics were compared in regard to their estradiol and prolactin plasma levels. For each group, the hormone values of the periovulatory phase (cycle day 10–12) were taken for comparison.

As expected, the mean prolactin serum level during the periovulatory phase in patients receiving conventional antipsychotics (1600 mU/l) is much higher than the upper range of the normal reference values of 410 mU/l. As expected, there is a statistically significant difference in prolactin serum levels between the group receiving conventional antipsychotics and patients receiving the atypical antipsychotics clozapine (p < 0.001) or olanzapine (p = 0.005); however, there is no statistically significant difference between the two atypical antipsychotics (Table 3; linear regression analysis with robust standard error, pairs group comparison in pairs by means of Wald-test with Sidak correction).

Table 3

<table>
<thead>
<tr>
<th>Group</th>
<th>Conventional antipsychotics (n=31)</th>
<th>Clozapine (n=11)</th>
<th>Olanzapine (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M ± S.D.</td>
<td>p</td>
<td>M ± S.D.</td>
</tr>
<tr>
<td>17β-estradiol (pg/ml)</td>
<td>65.6±61.0</td>
<td>n.s.</td>
<td>58.7±46.4</td>
</tr>
<tr>
<td>prolactin (mU/l)</td>
<td>1600±1278</td>
<td>&lt;0.001</td>
<td>467±170</td>
</tr>
</tbody>
</table>

* Conventional antipsychotics vs. olanzapine.
analysis with robust standard errors). Likewise, there is no significant effect of age, duration of illness, or number of hospitalizations on the differences in prolactin levels.

In contrast to this result, the mean serum estradiol levels were far below 100 pg/ml in all three groups. Only 19.3% of the patients receiving conventional antipsychotics and 27.3% receiving clozapine presented with serum estradiol levels over 100 pg/ml in the periovulatory phase. No statistically significant difference was found in mean serum estradiol levels between the patient groups receiving conventional antipsychotics and clozapine (65.6 vs. 58.7 pg/ml, cf. Table 3). However, the mean serum estradiol levels in the group receiving olanzapine (18.7 pg/ml) were significantly lower than in the two other groups (linear regression analysis with robust standard errors, cf. Table 3). The variables age and duration of illness, or number of hospitalizations as indicators of disease severity showed no effect on the estradiol serum concentration in the regression analysis.

4. Discussion

The data presented here show that, compared to normal reference values, serum levels of estradiol in premenopausal, menstruating women with schizophrenia were generally reduced during the entire menstrual cycle. Additionally, decreased progesterone plasma levels in the luteal phase indicated anovulatory cycles and insufficient follicle maturation. We found hypoestrogenism in 57.3% of the patients; that is, estrogen levels below 30 pg/ml in the follicular phase and below 100 pg/ml in the periovulatory phase of the menstrual cycle.

Compared to normal reference values, very low serum levels of estradiol could be shown in a subgroup of patients under only conventional (“typical”) antipsychotics as well as in a subgroup of patients being treated only with atypical antipsychotics (clozapine or olanzapine), i.e., under high versus low prolactin level conditions. Therefore, low serum levels of estradiol seem to be independent of antipsychotic-induced endocrine disturbances, in particular, independent of the elevation of prolactin levels. In the group treated with olanzapine, this effect was particularly apparent, and levels were statistically significantly reduced compared to the other two groups. As expected, prolactin levels were much higher in the group receiving conventional antipsychotics, with values up to tenfold higher than the upper range of normal, in contrast to significantly lower serum prolactin levels in the two groups receiving atypical antipsychotics.

Our findings support the hypothesis of primary hypoestrogenemia in women with schizophrenia, as have other studies investigating this. However, the reasons for a primary hypoestrogenism are not clear yet. Various reasons for this primary hypoestrogenism not related to antipsychotics-mediated hyperprolactinaemia and subsequent hyperthalamic feedback mechanisms-induced hypoestrogenism in women with schizophrenia have been suggested in the literature. Huber et al. (2001) explain part of the difference in estradiol levels between psychotic women and a group of healthy subjects by stress and deficient nutrition. The stress of an acute psychiatric illness and hospital admission would indeed cause a hypothalamic down-regulation, with acutely diminishing estradiol levels mediated through elevated blood cortisol levels. However, this explanation does not fit the patients enrolled in our study, who were not acutely hospitalized and in whom the condition had remitted before enrollment in the study.

Findings by Warner et al. (2001) showed that the prolactin levels in unmedicated schizophrenic patients were lower than in control subjects. The authors attribute this result to disturbances in the dopaminergic system because dopamine tonically inhibits prolactin. This result also indicates disturbances in the hypothalamic–pituitary–gonadal axis in schizophrenic women, which raises the question of whether a gonadal dysfunction with estrogen deficiency is even part of the underlying pathogenetic process in schizophrenia (Riecher-Rössler, 2003).

With the design of the present study, we were not able to clarify whether the onset of hormonal deficiencies appears before or only after the onset of illness. For this purpose, a different design would have been required, ideally, a longitudinal design. Onset of a hormonal imbalance early in life could explain disturbances in brain development, causing vulnerability for schizophrenia, as steroid hormones are known to act as organizers in the brain during critical periods of neuronal growth (McEwen and Alvers, 1999; cf. DeLisi et al., 1989).
Furthermore, an ideal study design here would be to examine the hormone levels of drug-naive patients, and preferentially without antipsychotics during an entire menstrual cycle; of course, this demand does not conform to ethical standards.

The age of the patients and the duration of illness or the number of hospitalizations had no effect on the estradiol serum concentrations. Further studies should also control for other factors that might influence the levels of gonadal hormones; for example, cigarette smoking, alcohol, and coffee consumption, or psychotropic drugs other than antipsychotics.

To achieve the objective of the present study, we had to determine the estradiol levels at different phases of the menstrual cycle because a single measurement of hormone levels at any point in time of the menstrual cycle would not provide any evidence; for example, results from one blood analysis at admission would be questionable because most schizophrenic women are hospitalized perimenstrually—this means during a phase of the cycle in which estradiol levels are very low (Bergemann et al., 2002; Huber et al., 2001)—and this value cannot be considered indicative of overall estradiol levels throughout the entire cycle. Therefore, the hormone blood levels were assessed three times during the cycle on the indicated cycle days—at cycle days 2–4, 10–12, and 22–24, representing the follicular, the periovulatory, and the luteal phase. This procedure might be criticized as being overly standardized; however, it can be justified as all patients included in the study described their menstrual cycle as “regular”—although our results suggest hypoestrogenism and anovulatory cycles in most of the patients. An ideal procedure would be to define the individual cycle phases for each patient by obtaining several blood samples during the menstrual cycle, which would provide a better approximation to the point in time which represents the respective cycle phases for each patient.

From a therapeutic point of view, the results presented here are of particular interest. As mentioned above, empirical evidence was found in previous studies for a protective effect of estrogen in schizophrenia, which suggests its use in treatment and prophylaxis. An estrogen supplement could be particularly effective in those women with schizophrenia suffering from hypoestrogenemia. However, only very few studies addressing this issue have been conducted to date (Kulkarni et al., 1996, 2001; Kulkarni, 2004; Bergemann et al., 2004a; Lindamer et al., 2001). More interventional trials, ideally, with a double-blinded and placebo-controlled design which considers the estrogen status of the patients, should be carried out. In this context, possible risks of estrogen therapy have to be assessed (cf. The Writing Group of the International Menopause Society Executive Committee, 2004; The North American Menopause Society, 2003; Writing Group for the Women’s Health Initiative Investigators, 2002; Notman and Nadelson, 2002; Turgeon et al., 2004).

Last but not least, an issue which is of high interest and should be addressed in further studies is the question of whether schizophrenic women suffer from long-term hypoestrogenism. This is of particular value as somatic problems secondary to hypoestrogenemia in schizophrenic women such as osteoporosis or cardiovascular risks might result, which could require specific therapy.

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