Can Estradiol Modulate Schizophrenic Symptomatology?

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Abstract

Using epidemiologic data, in an earlier study we formulated the hypothesis that estrogens can delay the onset of schizophrenia in females by raising the vulnerability threshold for this disease. In animal experiments, Häfner and colleagues found evidence that chronic estradiol treatment reduces the sensitivity of dopamine (D_2) receptors in the brain.

In the clinical study presented in this article, as a further step we examined the antipsychotic properties of estradiol in human females by testing whether schizophrenic symptomatology varies with estradiol serum levels throughout the menstrual cycle. We examined 32 acutely admitted female schizophrenia patients (Present State Examination/ CATEGO diagnosis, ICD-9) with a history of regular menstrual cycles, ages 18 to 43 (mean = 30.5), during their hospital stays (3–8 weeks), analyzing hormonal parameters and applying various rating scales for psychopathology every 7 days. In all patients, estradiol serum levels were markedly reduced as compared with the normal population, and fluctuations throughout the cycle were dampened. Nevertheless, a significant association emerged between estradiol levels, on the one hand, and psychopathology scores, on the other—that is, the psychiatric symptomatology as assessed by the clinical psychiatrist (Brief Psychiatric Rating Scale, $p \leq 0.01$), behavior on the ward as assessed by the nursing staff (Nurses' Observation Scale for Inpatient Evaluation $p \leq 0.01$), paranoid tendencies and general well-being as assessed by the patients themselves (Paranoid-Depressivitäts-Skala paranoid score $p \leq 0.05$; Befindlichkeits-Skala $p \leq 0.05$). Psychopathology seems to improve when estradiol levels rise, and vice versa. These findings can be interpreted as further evidence for a protective effect of estrogens in schizophrenia, possibly due to the known antidopaminergic activities of these hormones.

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The ABC study is an epidemiologic investigation of schizophrenia with special emphasis on sex differences in this disease. We examined different populations in the framework of this study and found that females, in comparison with males, not only had a delayed peak for illness onset, but also exhibited an additional, smaller incidence peak after age 40–45. These peaks are also found using the earliest definition of onset (Häfner et al. 1989, 1991*c*, 1992). This result was interesting because, when planning our study, Häfner had put forward several psychosocial and biological hypotheses for explaining gender differences in schizophrenia. One hypothesis was "that the threshold of vulnerability for schizophrenia is higher in females than in males because of the modulating effect of estrogen on the dopamine activity" (Häfner 1987, p. 69).

Assuming that genetically predisposed, vulnerable individuals fall ill as soon as (intrinsic or extrinsic) stress factors increase or

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(intrinsic or extrinsic) protective factors decrease, estrogens may be one such intrinsic protective factor. In this case, women would, to some extent, be protected against schizophrenia between puberty and menopause by their high estrogen levels. This difference might explain the delayed and lower first-onset peak in females as compared with males. As the physiological estrogen production decreases in the years before and during menopause, this protective factor would weaken considerably, which might account for females' additional peak after age 40–45. Thus, our epidemiologic data might well be explained by the sex hormone hypothesis, which itself can be situated within a long tradition.

Only recently have some authors (e.g., Seeman 1981, 1983; Häfner 1987; Lewine 1988; Seeman and Lang 1990; Häfner et al. 1991*a*, 1991*b*, 1991*c*; Riecher et al. 1991; Riecher-Rössler and Häfner 1993) readdressed the estrogen hypothesis in association with schizophrenic psychoses, since there is now increasing evidence for an antipsychotic effect of estrogens. The neuroendocrinologic basis for this effect seems to be a modulating effect of estrogens on the dopaminergic systems. One can find the following conclusions in the literature.

- The presence of estrogen receptors in the limbic system indicates that estrogens not only play a part in the modulation of endocrine functions but also have a neuromodulatory function (Holsboer 1983; Lobo et al. 1984; Maggi and Perez 1985).
- Estrogens can reduce the dopamine (DA) concentration in the striatum (Foreman and Porter 1980; Dupont et al. 1981) and modulate the sensitivity as well as the number of DA receptors (Koller et al. 1980; Gordon and Diamond 1981; Bédard et al. 1984).
- In laboratory animals, estrogens can enhance neuroleptic-induced catalepsy (Gordon et al. 1980; DiPaolo et al. 1981; Nicoletti et al. 1983) and reduce amphetamine- and apomorphine-induced behavior (stereotypies, etc.) (Gordon et al. 1980; Hruska and Silbergeld 1980).
- Clinically, there are case reports on women whose psychotic symptomatology exacerbates mainly premenstrually—that is, when estrogen levels drop (Endo et al. 1978; Glick and Stewart 1980).
- During pregnancy, on the other hand, a time of extremely high estrogen levels, chronic psychosis such as schizophrenia seems to improve (Chang and Renshaw 1986).
- After delivery, when estrogen levels drop dramatically, an increased vulnerability for psychoses is observed (Nott 1982; Kendell et al. 1987).
- Female schizophrenia patients between ages 20 and 40 require lower doses of neuroleptics than older females or males of the same age group (Seeman 1983).
- Estrogens show a positive clinical effect in neuroleptic-induced dyskinesia, probably because of their antidopaminergic properties (Bédard et al. 1977; Villeneuve et al. 1980).
- Estrogens may have additional effects on other neurotransmitter systems, but these effects are not the subject of this article.

Thus, the estrogen hypothesis not only provides an excellent explanation for our epidemiologic data, but is also based on numerous findings of clinical and basic research. Although there is no conclusive evidence for the increase of dopaminergic activity in the brains of schizophrenia patients (Gattaz et al. 1983; Carlsson 1987), schizophrenic symptoms—at least the productive ones—can be successfully treated and suppressed by substances blocking DA transmission in the brain. Estrogens may therefore exert their positive effect in schizophrenia by their antidopaminergic properties.

Häfner et al. (1991*a*, 1991*b*) further examined the neurohormonal effects of estradiol by means of animal experiments. Concerning the estrogen hypothesis, the results only partly met expectations: Prolonged estradiol administration attenuated most of the behavior induced by DA agonists and antagonists. That this effect was more marked in newborn than in adult rats suggests a "structural" effect of physiologic estradiol concentration on the dopaminergic system during brain development (Häfner et al. 1991*a*, 1991*b*). However, there was also a "functional," though less marked, effect of estrogens in adult brains, indicated by a decrease in dopamine receptor affinity for [^{3}H]sulpiride. Together, those findings lead to the assumption that estradiol downregulates the D_2 receptors in the brain (Häfner et al. 1991*a*, 1991*b*; Gattaz et al. 1992).

Thus, starting with our epidemiologic findings and encouraged by the results of the animal study, we tried to test the estrogen hypothesis in a clinical study. Since an intervention study with estrogens was not justifiable at such an early stage of research, we chose the female menstrual cycle as a "natural experiment." Throughout the

menstrual cycle, the ovarian estradiol production in fertile women shows strong fluctuations directly measurable in the blood. Moreover, estradiol has easy access to the brain, and concentrations of estradiol in plasma and cerebrospinal fluid are highly correlated (Bäckström et al. 1976).

The clinical study starts with the hypothesis that schizophrenic symptomatology varies with the menstrual cycle—that is, that symptoms in women with schizophrenia are more likely to occur or be exacerbated at times of low estrogen blood levels (premenstrual and menstrual phases) than at other phases of the cycle. In particular the following hypothesis was to be tested: The variation of the estradiol level during the menstrual cycle shows a negative correlation with the schizophrenic symptomatology during an acute episode; that is, the patients' symptoms decrease when serum estradiol levels increase and vice versa.

Methods

Sample. All females with a clinical diagnosis of schizophrenia consecutively admitted to Pfalzklinik Landeck from June 1, 1988, to April 30, 1989, were screened. Inclusion criteria were age range 18 to 45; acute onset or relapse of psychosis and acute admission; regular menstrual cycles; no endocrine disease or suspected organic brain syndrome; operationalized diagnosis of schizophrenia according to the International Classification of Diseases (ICD-9; World Health Organization 1978), based on the Present State Examination and the corresponding computer program CATEGO (Wing et al. 1974). Of 54 patients who fulfilled these criteria, 8 refused to participate, and another 14 were not able to give informed consent or to participate because of severe illness; 32 patients could be included in the study.

The patients examined were on average 30.5 years old (standard deviation [SD] = 6.5; range = 18–43). Nine were being admitted for the first time. On average, first psychiatric hospitalization had taken place 2.5 years before the present admission. The patients' *stated* mean cycle length was 27.1 days (range 23–32). The *observed* cycle length varied between 11 and 66 days (average: 28.4 days). All but six patients had taken neuroleptics the week before hospitalization. Also, during their hospital stay they were treated with neuroleptics and other psychopharmacologic drugs by independent clinicians. Medication was documented precisely. Five patients had taken hormonal contraceptives, which they had stopped in the weeks preceding admission.

Study Design. Each female was examined beginning with hospitalization over at least one complete menstrual cycle. Psychopathology and various hormone parameters were evaluated on the day of admission as well as on the 2nd, 7th, 13th, 14th, 21st, and 28th days of the menstrual cycle (i.e., at least every 7 days, with an additional midcycle measurement). The cycle days were fixed at first on the basis of menstrual history but as soon as possible on the basis of the observed menstruation, which very often occurred with admission. On the defined days, the following measurements were undertaken:

- *Psychopathology:* General psychiatric symptomatology was assessed by the clinician using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). Patient's behavior was assessed by the nursing staff using the Nurses' Observation Scale for Inpatient Evaluation (NOSIE; Honigfeld et al. 1976). Paranoid and depressive tendencies as well as general well-being were assessed by the patients themselves using the Paranoid-Depressivitäts-Skala (PDS; von Zerssen and Koeller 1976) and the Befindlichkeits-Skala (BFS; von Zerssen and Koeller 1976). Menstrual history and psychopathology were assessed in the same patient independently, and the doctor and the nurse assessing psychopathology were blind to the patient's cycle. The patients were not aware that their menstrual cycles were being correlated to symptoms.
- *Laboratory:* On each assessment day estradiol and progesterone were measured, and on the second day of menstruation prolactin and testosterone were also measured. Blood was taken in a standardized manner every morning before medication; serum was kept frozen at –40 °C. Once all examinations in the 32 patients were finished, all laboratory analyses were carried out in a single batch to avoid methodologic variation. Immunoassays were used.

Statistical Procedures. To determine the association between estradiol blood levels and psychopathology scores during the hospital stay, cross-correlations (Jenkins and Watts 1968) were calculated. The cross-correlation function is well established in electroencephalographic analysis and in engineering as a measure of similarity between two curves. For each individual we calculated

cross-correlations between the estradiol curve and the curves of the different psychopathology scores. In this case, the correlation coefficients are parameters for the similarity between the estradiol curve and the five total score curves of the different rating scales in each individual. Subsequently, Wilcoxon tests were calculated over the group as a whole to determine the significance of the associations.

Results

Hormonal Status.

Normal values. To allow comparisons, the normal values of the hormones analyzed will be given first. They were established in the Institute of Clinical Chemistry of the University of Mannheim/Heidelberg, where the analyses for our study were undertaken as well, and refer to large samples of healthy, fertile women:

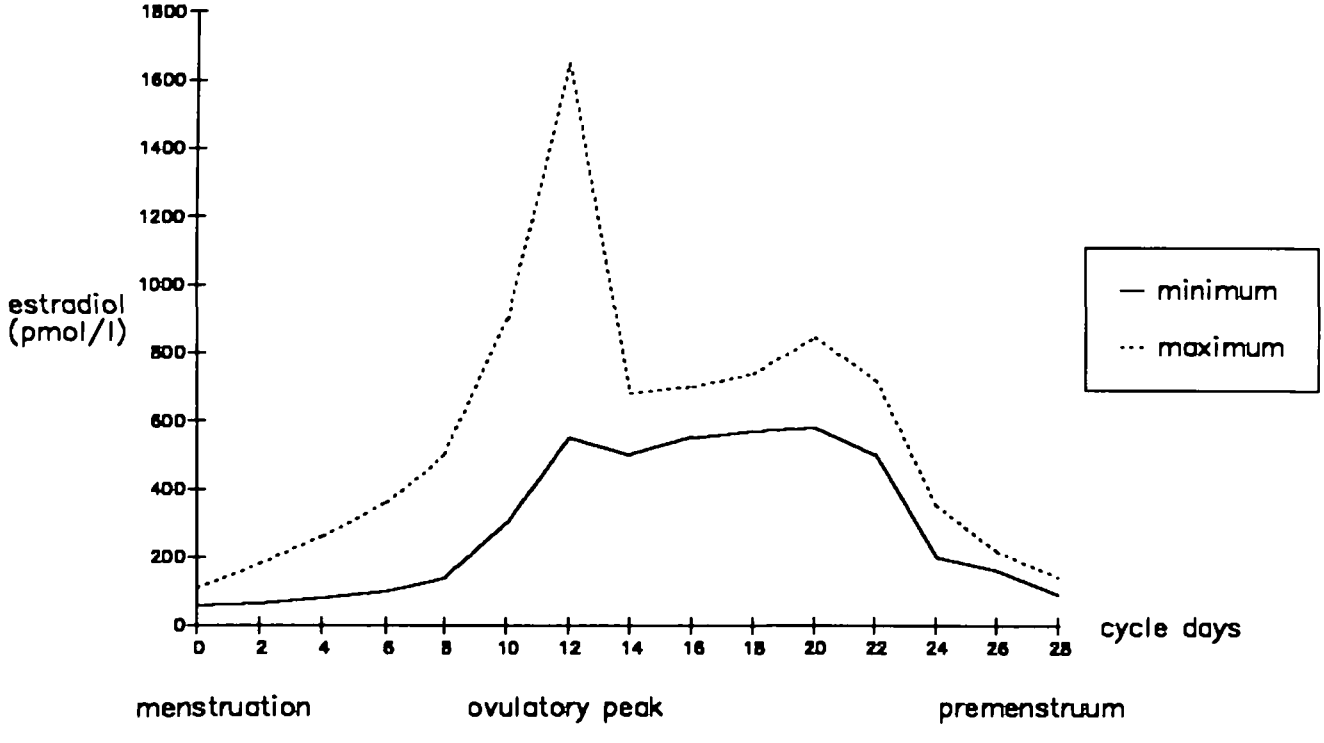
- *Estradiol:* preovulatory phase, 90–1,660 pmol/L; preovulatory peak, 550–1,660 pmol/L; postovulatory phase, 550–845 pmol/L.
- *Progesterone:* preovulatory phase, 0–4.5 nmol/L; postovulatory phase, 15.9–95.4 nmol/L.
- *Prolactin:* 2.3–15.9 ng/mL.
- *Testosterone:* 0.5–4.0 nmol/L.

These values as well as those of our study can be regarded as highly reliable because the quality of analyses using these assays in this laboratory is confirmed in quarterly external controls (ring trials). Further, pool and control sera are used for each series of analysis and other modern standards of radioimmunoassay technique are taken into consideration.

Figure 1 shows the normal variation in the estradiol level during a normal ovulatory cycle of 28 days. These data are based on probes of 350 healthy, unmedicated, fertile women with regular cycles.

Values in schizophrenia patients. Prolactin and testosterone were measured at day 1 or 2 of the menstrual cycle. All but six patients showed hyperprolactinemia (mean = 43.1 ng/mL). One patient had an increased testosterone level (4.8 nmol/L). Clinically,

Figure 1. Normal range of the estradiol level during a normal ovulatory cycle of 28 days*



* normal values of the Institute of Clinical Chemistry, University of Mannheim

she showed no signs of virilization. All the other patients had normal testosterone levels (mean = 1.8 nmol/L).

In only two patients the progesterone values *at admission* (mean = 4.3 nmol/L) exceeded 15.9 nmol/L, indicating a postovulatory phase. The estradiol values at admission ranged from 45 to 502 pmol/L (mean = 176.5 pmol/L), clearly within the lower part of the cycle-dependent normal range. No patient showed values over 550 pmol/L, which would indicate normal follicular maturation with ovulation.

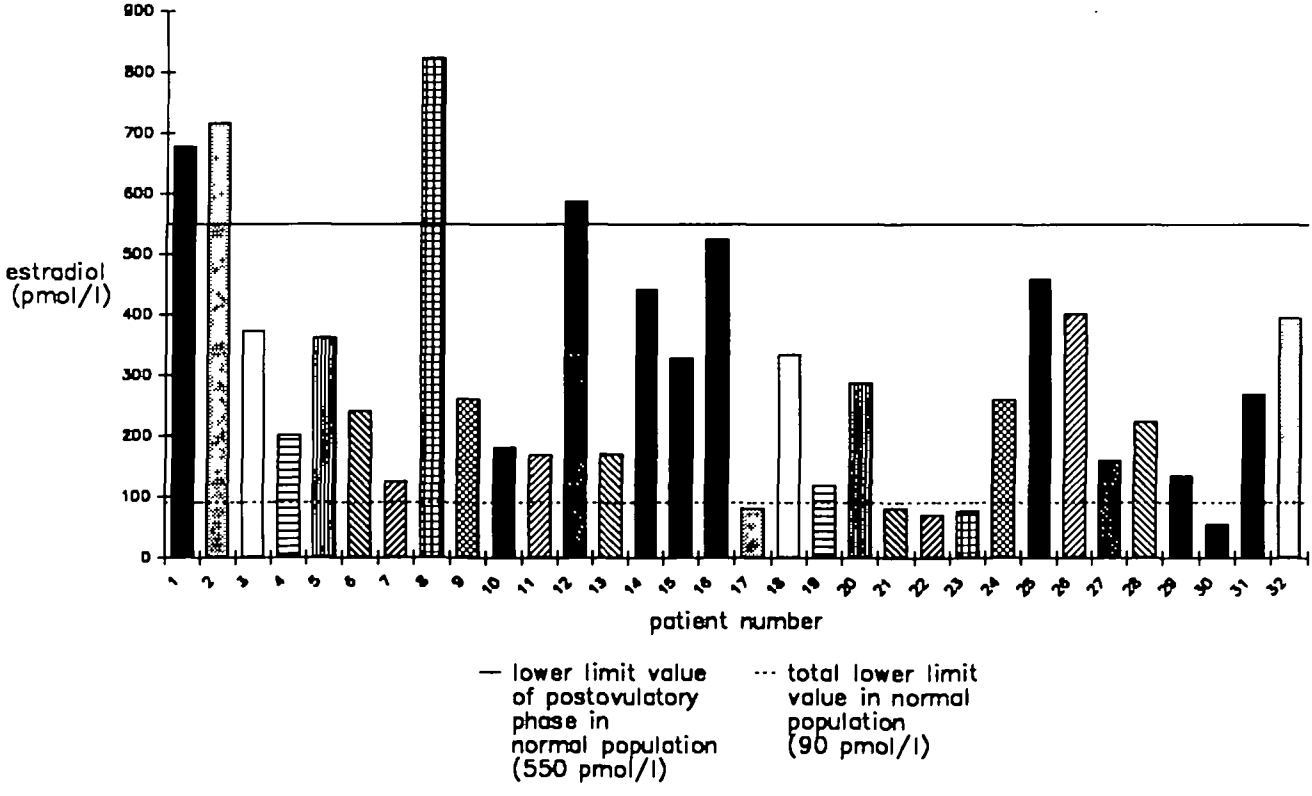
Figure 2 presents the highest estradiol values observed in each patient *over the whole observation period* (3–8 weeks). The patients' maximum estradiol value was 824 pmol/L. So, none of them reached the upper area of the normal range.

During the whole study period only 6 of the 32 patients ever had progesterone values exceeding 15.9 nmol/L, indicating normal luteal function after ovulation. In another seven individuals the highest values were within the marginal range (4.5–15.9 nmol/L).

When prolactin, estradiol, and progesterone were assessed together in each patient, only 14 patients could be considered to have had an ovulatory cycle. Five of the 14 presumably suffered from corpus luteum insufficiency. Eighteen patients appeared to have had anovulatory cycles. In all patients—including those who had ovulatory cycles—the estradiol production was markedly reduced as compared with the normal population, with the serum levels varying only slightly throughout the cycle.

Association Between Estradiol Serum Level and Symptomatology. To examine whether psychiatric, and especially schizophrenic, symptomatology varies with serum estradiol levels during the menstrual cycle, for each individual and her complete inpatient period we evaluated the association between the serum estradiol curve

Figure 2. Highest estradiol level observed during hospital stay



and the different curves of specific and unspecific psychopathology. As was outlined in the methods section, we calculated cross-correlations between the individual curves of each woman separately. We thus got five association parameters per woman: estradiol correlated with each of BPRS, NOSIE, BFS, PDS paranoid score, and PDS depression score. The association parameters vary between women. Table 1 shows for each association parameter the mean value and SD for the 32 women. The mean values are all negative, except for NOSIE, whose higher value, in contrast to the other scales, means *less* pathology. And all mean values (except that for depression) deviate significantly from zero (one-sided Wilcoxon test).

Thus, symptomatology seems to improve when estradiol levels rise, and vice versa. This is true for psychiatric symptomatology (BPRS) as assessed by the clinical psychiatrist, for the general behavior on ward as assessed by the nursing staff (NOSIE), and for the areas "paranoid tendencies" (PDS paranoid score) and "general well-being" (BFS), both of which are assessed by the patients themselves.

An analysis of the BPRS subscores pointed in the same direction. There was an inverse association for all subscores except "anxiety/depression": thought disturbance, $p \leq 0.01$; activation, $p \leq 0.01$; anergia, $p < 0.10$; and hostile-suspiciousness, $p < 0.10$. As "thought disturbance" is a subscore with mainly psychotic items, this result indicates that estradiol levels are inversely associated not only with general psychiatric symptomatology, but also, especially strongly, with psychotic symptoms.

As we have shown, our patients' estradiol levels were very low and showed only slight cyclical variations. And when a parameter varies only a little, it is difficult to identify associations with other parameters. Nevertheless, these inverse associations could be seen. Only for the patients' self-assessed change in depressiveness was the association with estradiol not significant, a finding that agrees with the hypothetic neuroleptic-like effect of estradiol. Figure 3 shows the profiles of estradiol and the different psychopathology scores for one patient as an example.

In the next step, only those 14 patients whose estradiol levels showed variations of at least 200 pmol/L over the whole cycle were included in the analysis. In this subsample, the association between estradiol and psychopathology was quantitatively even stronger, though less significant because of the lower number of patients.

Table 1. Means of individual correlation coefficients between estradiol curves and psychopathology (n = 32)

	Mean (SD)	p
BPRS, total score	−0.25 (0.41)	0.002
NOSIE, total score[1]	0.25 (0.49)	0.004
BFS, total score	−0.20 (0.43)	0.032
PDS, paranoid score	−0.17 (0.42)	0.029
PDS, depression score	−0.10 (0.52)	0.277 (NS)

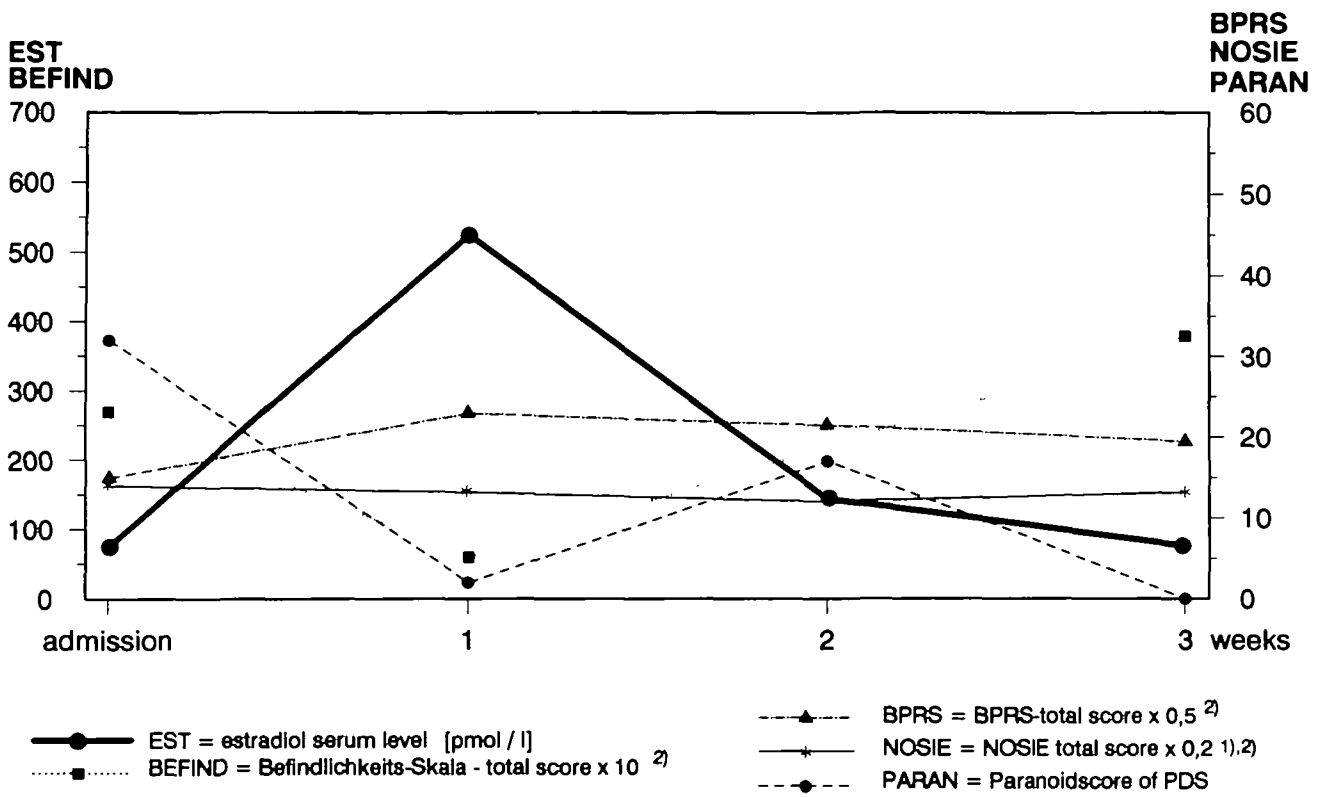
Note.—SD = standard deviation; BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962), NOSIE = Nurses' Observation Scale for Inpatient Evaluation (Honigfeld et al 1976); BFS = Befindlichkeits-Skala and PDS = Paranoid-Depressivitäts-Skala (von Zerssen and Koeller 1976); NS = not significant.

[1]Unlike the other scores, in the total NOSIE score a higher value means *less* psychopathology.

Discussion

The observation of 32 women with schizophrenia over their whole hospital stay showed that most of the patients, when compared with normal women, exhibited markedly lowered estradiol production, with only minor variations in estradiol serum levels during their cycle. Despite this, and despite a potential masking by different factors of influence such as neuroleptic dose adjustment, a significant relationship between the estradiol level and various psychopathology scores became evident: With increasing estradiol levels, symptomatology improved; with decreasing estradiol levels, it deteriorated. This was true for the general psychiatric symptomatology (as assessed by the doctor), the behavior on the ward (as assessed by the nursing staff), and general well-being and paranoid tendencies (which the patients assessed themselves). Only the self-assessed depressiveness failed to show any significant association. This finding meets our theoretical expectations deduced from animal experiments: If estrogens alter the sensitivity of D_2 receptors in the brain (i.e., if they have a neuroleptic-like effect),

Figure 3. Course of estradiol serum level and different psychopathology scores during hospital stay—Example of one patient



1) The higher the different psychopathology scores, the more severely disturbed is the patient. The NOSIE - Index curve had to be mirrored for this purpose.
2) Some scores had to be multiplied by a factor in order to fit them into one diagram.

Note.—Some scores had to be multiplied by a factor to fit them into one diagram. The higher the different psychopathology scores, the more severely disturbed is the patient. The NOSIE curve had to be mirrored for this purpose.

an antidepressive effect is not necessarily to be expected.

Our findings raise various questions. First, it is of interest to know the strength of the effect. The correlation coefficients used as a measure of association between the estradiol and the psychopathology profiles are on average not very high, but they deviate significantly from zero. Here, one has to bear in mind that our patients' estradiol levels showed only minor variations. And if despite only minor variations of one parameter, there is a significant relationship to other parameters, this relationship must be a clear one. Also, the effects were quantitatively stronger in the subgroup of women whose estradiol variations were more marked; that the effects were not more significant in this subgroup is probably because of the small number of patients. Our results therefore seem to indicate that the influence of estrogens is not negligible. A larger group of patients should be studied, though.

Further questions concern the specificity of our results:

- *The specificity of estradiol as an influencing factor:* Is it really estradiol that accounts for the variations of symptomatology, and not other factors?

• *The specificity of the dependent factor (i.e., psychopathology):* (1) Is it only the symptomatology of schizophrenia that is subject to estradiol-dependent variations, or is it also the mental state in other diseases and in the healthy? (2) In schizophrenia patients, is it only the nonspecific symptoms, or also the specific, psychotic symptoms that are influenced by estradiol?

Regarding the first question, it cannot be ruled out that the association between estradiol level and symptomatology is due to other, covarying factors. Among those factors the most important may be neuroleptics, the dosage of which depends in part on the symptomatology. Neuroleptics could theoretically suppress the ovarian estradiol production through hyperprolactinemia. The fact, however, that long-term hyperprolactinemia can suppress ovarian estradiol production is known only from inquiries into hyperprolactinemia of *other* etiology (Diedrich and Wildt 1990). As to a potential influence of *neuroleptics* on estrogens, most studies have been performed before the advent of radioimmunoassays. Findings were often inconsistent and contradictory (for reviews see Shader and Di Mascio 1970; Beumont and Bergen 1982). Beumont et al. (1974*a*, 1974*b*) using radioimmunoassay in a longitudinal study of psychiatric inpatients receiving neuroleptics found estrogen levels to be in the normal range in premenopausal women without amenorrhea as well as in postmenopausal women. Even in premenopausal women with amenorrhea, estrogen values were in the normal range for the follicular phase of the cycle. For schizophrenia, Prentice and Deakin (1992) recently showed that there is no difference between patients with and without menstrual irregularities in total neuroleptic dosage or serum prolactin concentration. These findings speak against neuroleptics being the major determining influence on menstrual irregularities and on estradiol production. In a comprehensive review on long-term effects of neuroleptic drugs, Meltzer (1985) stated: "[similar] difficulty in attributing sexual dysfunction such as amenorrhea, or abnormalities in sex hormone serum levels in female schizophrenics to neuroleptic treatment rather than to the illness per se [also exists]" (p. 60).

In our own study we could find no association between neuroleptics and estradiol serum levels, either interindividual or intraindividual. Among individuals, there was no correlation between mean neuroleptic dosage (in chlorpromazine equivalents) and mean estradiol level during hospital stay (r = −0.14; p = NS). The average neuroleptic dose during hospital stay was about the same for patients with and without ovulation (815.3 and 757.5 chlorpromazine equivalents; p = NS, t test). Nor did testing intraindividually by calculating cross-correlations between neuroleptic dosage and estradiol curves reveal any significant association. These facts speak against a direct influence of neuroleptics on the estradiol serum level.

Apart from that, it is not to be expected that a complex chain of reactions like symptom deterioration leading to increase of neuroleptic dose leading to increase of prolactin blood levels leading to decrease of estrogen blood levels would go on without a time lag. Therefore, the *direct* temporal association between estradiol level and symptomatology shown in table 1 also speaks against causation by such an intermediate factor. Thus, it seems unlikely that the inverse association between estradiol and symptomatology is mediated through neuroleptics.

As to the specificity of estradiol's effects for schizophrenia, there is also evidence for cycle-dependent variations of well-being in many healthy women, known as premenstrual syndrome. The relationship between this syndrome and the estradiol level has been discussed but not yet proved. Results from the large number of studies are very inconsistent in terms of etiology (Rubinow and Roy-Byrne 1984). We do not know of any corresponding studies for the mentally ill that include direct measurement of estradiol levels.

Finally, we could show in our schizophrenia patients that not only are unspecific symptoms and general behavior associated with cyclical variations of estradiol, but psychotic symptoms and paranoid tendencies are also related. In schizophrenia patients, estradiol seems to have clear antipsychotic properties in addition to a general stabilizing effect.

Another important point to discuss is that we observed a marked excess of admissions during the low-estrogen phase of the cycle. In fact, 16 of 28 patients in whom we could exactly determine the cycle phases were admitted in the low-estrogen third of their cycle, defined as the third of the cycle starting 3 days before menstruation onset ($p \leq 0.01$). Therefore the question arose whether this overrepresentation could account for the correlations found. However, this would only be a problem if all patients had the same cycle

length and the same duration of treatment until symptom improvement, which was not the case: Symptom improvement took 3 to 8 weeks (observation period), and the cycle lengths of the 32 patients included in the analysis varied between 11 and 66 days. Thus, with maximum symptom improvement at the end of their hospital stay the patients were in different cycle phases and had different estradiol levels.

A secondary finding of our study also requires some explanation. Many female schizophrenia patients exhibited considerable cyclical disturbances; for that reason several patients acutely admitted during the study period failed to qualify for our study. Most of the examined patients appeared to have reduced estradiol levels compared with normal females, and in some of them these low levels were obviously linked with anovulatory cycles. As we have discussed above, this might not be due to neuroleptic treatment only. Furthermore, the fact that "hypoestrogenism" in women with schizophrenia was observed before the discovery of neuroleptics (e.g., Kretschmer 1921/1967; Bleuler 1943) implies that those disturbances may be a primary part of the schizophrenia process. Our study was not designed to test this question, and we may have missed higher hormone values because of infrequent measurements. But in our opinion there are enough indications of hypoestrogenism in schizophrenia patients to justify further investigations (for review see Riecher-Rössler and Häfner 1993).

Provided our results are confirmed by replication, they may be relevant to research as well as to the clinic. First, our findings further confirm the hypothesis proposed by Häfner (1987) to explain gender differences in age at onset in schizophrenia: Women predisposed to schizophrenia would be particularly protected from the onset between puberty and (pre-)menopause, when their physiological ovarian estrogen production is high. In some women the illness onset would be delayed even until menopause, when protection by estrogens disappears.

Moreover, our results show that the protective effect of estradiol in fertile women varies not only over the female life cycle, but also over the menstrual cycle; that is, if the disease occurs, it occurs mostly in the phase when estradiol levels are low. And during an episode, psychopathology varies with serum estradiol levels throughout the menstrual cycle.

The mechanism of this effect seems to be similar to that of major tranquilizers, since apart from a general stabilization, an antipsychotic effect can also be observed. Thus, our clinical study can be regarded as a confirmation of the findings from our animal experiments, which indicated that estradiol can have a neuroleptic-like effect by altering the sensitivity of D_2 receptors in the brain. The study goes beyond the animal experiments in that it also suggests effects of estradiol in humans. And it goes beyond our epidemiologic results, which only indicated an influence of estrogens on age at onset and thus on the *vulnerability threshold* for the outbreak of the disease: The study on the menstrual cycle also demonstrates a direct influence of estradiol on the *intensity of the symptomatology*.

Last but not least, our results may have clinical relevance for therapy and relapse prevention. First, in treating young women with schizophrenia, one could adjust the neuroleptic dose to the menstrual cycle to give higher doses during perimenstruum and lower doses intermenstrually. Thus, perimenstrual exacerbations might be avoided; at least, the overall neuroleptic dose could be lower and yet have the same therapeutic and relapse-preventing effect, which would have the advantage of fewer side effects. This approach could be especially worthwhile in the subgroup of women with a perimenstrual excess of relapses.

Second, menopausal and postmenopausal women could undergo a hormonal substitution treatment, similar to the one used against osteoporosis. Here, one has to bear in mind that estrogen levels begin to fall years before the last menstruation. Corresponding intervention studies should be carried out in the next step. In the long run, such a "cycle-modulated" neuroleptic dosage in fertile women on the one hand, and "adjuvant" estrogen therapy in women before and after menopause, on the other, could—at least in women—have a positive influence on the course of schizophrenic disorders.

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Announcement

The International Health Society and the World Association for Social Psychiatry will sponsor a conference entitled **Medicine and Psychology in a Holistic Approach to Health and Illness.** The conference will be held October 25–29, 1994, in St. Petersburg, Russia. Topics to be covered include: theory and methodology of the systems approach to health and illness; holistic approach to understanding and treatment of the patient in dynamic psychiatry; psychosocial aspects of prevention, treatment, and rehabilitation; psychosomatic problems of modern medicine; psychotherapy: theory and practice; psychotherapy and psychopharmacology; and legal and ethical aspects of psychiatry.

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