REVIEW PAPERS

The Role of Estrogen in Schizophrenia

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This paper reviews 3 recent studies from different clinics correlating psychotic symptoms with phases of the menstrual cycle in women with schizophrenia. The aim of the paper is to focus on the estrogen protection hypothesis which would suggest that low estrogen phases correlate with more severe symptoms, and high estrogen phases correlate with less severe symptoms. Although the methodology of the 3 studies was different, the hypothesis was essentially upheld. High levels of estrogens protect against symptom exacerbations in women with schizophrenia. A corollary to this finding is that, for optimal efficacy and safety, neuroleptic doses could be reduced at certain times of the month and increased at others.

Key Words: schizophrenia, estrogen, hormones, women

INTRODUCTION

A theory of "protection" from schizophrenia conferred by estrogens has emerged in the last 15 years based on epidemiologic, neurochemical, anatomic, and treatment response data (Häfner and others 1991, 1992; Lewine and Seeman 1995; Riecher-Rössler and others 1993, 1994; Seeman 1995; Seeman and Lang 1990).

Estrogens, like all gonadal steroids, are fat soluble and, thus, easily enter nerve cells and bind to specific receptor proteins either within the cell nucleus or in the cellular cytoplasm. These receptor-hormone complexes attach themselves to specific regulatory sequences of DNA which, in turn, either enhance or diminish the expression of specific protein-encoding genes (McEwen 1991). Such interactions frequently lead to progressively larger ripple effects, since the product of an enhanced gene may then go on to activate other genes. An example of this interaction is the effect of estradiol on genes that code for neurotrophic factors essential for the functional maintenance of neural communication (Toran-Allerand 1990). As far as is presently known, the chronology of estrogenic effects on neural plasticity suggests that the mechanism of estrogen's action is through gene expression. But estrogens may also act directly on neurotransmitter systems by effects at receptor sites or post-receptor sites such as G proteins. Of particular importance to schizophrenia, estrogens are known to modulate the dopamine system (DiPaolo 1994; De Vries 1990; Häfner and others 1991a, 1991b).

Interest in estrogens was first aroused by clinical and epidemiologic observations of male and female differences in the expression of schizophrenia (Seeman and Lang 1990). For instance, onset of illness is delayed in women by a mean of 4 to 6 years (Angermeyer and others 1989; Castle and

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others 1993; Hambrecht and others 1992), but this is only true if the illness starts after puberty (Galdos and others 1993). This finding suggests that the initiation of cyclical hormone fluxes in women may serve as a protective function against the development of adolescent psychosis. This possibility is reinforced by the observation that, whereas men exhibit 1 main peak of schizophrenia onset in their late teens and early twenties, women show an additional onset peak at age 40 to 45 years, which is a time when estrogen levels are falling (Häfner and others 1989, 1993; Hambrecht and others 1992; Riecher-Rössler and Häfner 1993).

In the same vein, although the severity of illness expression in women is less debilitating than in men during the first decade following onset (Biehl and others 1986; Goldstein 1988; Leff and others 1992; Pakaslahti 1992; Prudo and Monroe-Blum 1987; Salokongas and Stengard 1990; Thara and Rajkumar 1992), it approximates that of men (or becomes paradoxically more severe) in subsequent years, once any given cohort passes through menopause (Jonsson and Nyman 1991; Lloyd and others 1985; Opjordsmoen 1991). Furthermore, effective response to standard neuroleptics is said to take place at lower doses in women, at least premenopausally (Nedopil and others 1983; Seeman 1983). Postmenopausally, women require higher maintenance doses than men. This has been attributed to the potentiating effect of the antidopaminergic action of estrogen on neuroleptic response (Riecher-Rössler and Häfner 1993; Seeman 1989). Sex and age differences in extrapyramidal effects and tardive dyskinesia also suggest possible hormonal effects (Ayd 1960; Chakos and others 1992; McCreadie and others 1992; Swett 1975; Yassa and Jeste 1992), especially since tardive dyskinesia is alleviated by estrogen treatment in both sexes (Nelson and others 1995; Villeneuve and others 1980).

Other reported schizophrenia differences in men and women include different symptoms (Dworkin 1990; Franzek and Beckmann 1992; Goldstein and Link 1988; Rector and Seeman 1992; Shtasel and others 1992), brain structures (Lieberman and others 1992; Lewine and Seeman 1995), premorbid competencies (Bromet and others 1974), ratios of maternal second trimester viral infections (Takei and others 1993,1994), and birth complications (Lewis 1992). Women with schizophrenia appear to have more affected first-degree relatives than do men (Goldstein and others 1990, 1992; Maier and others 1993; Wolyniec and others 1992), a finding which does not lend itself to easy interpretation.

Further unsystematic clinical observations that are consistent with an estrogen influence are the reports of premenstrual exacerbations of schizophrenia, improvement of symptoms during pregnancy, aggravation of symptoms in the immediate postpartum period and at menopause (Chang and Renshaw 1986; Gerada and Reveley 1988; Kendell and others 1987).

Three studies (Hallonquist and others 1993; Riecher-Rössler and others 1994; Gattaz and others 1994) have tested the hypothesis that fluctuations in symptoms in women suffering from schizophrenia correlate with estrogen level. The prediction was that higher estrogen levels would be associated with milder symptoms; lower levels with more severe symptoms. Specifically, the hypothesis of all 3 studies was that the putative protective effect of estrogens would be apparent over the course of naturally occurring menstrual cycles.

METHODS

The Hallonquist and others' (1993) population base was a registry of patients with schizophrenia diagnosed by DSM-IlI-R criteria using the SCID interview (Spitzer and Williams 1985). The registry consisted of subjects from outpatient clinics or private practices in Toronto who had previously agreed to be recruited for research studies. Twenty-five of sixty-six registrants at the time this study was conducted were women. All were asked to participate; 22 agreed. Of these women (aged 29 to 49 years), 5 were asked to take part in an initial pilot task to see if they could fill out a daily symptom checklist at home over a 2-month period. The 5 women were successful at completing the task. Of the 17 remaining subjects, only 10 were menstruating. They all entered the study but only 5 had 2 consecutive cycles of under 35 days' duration during the study period. These 5 subjects constituted the study sample.

Thus, the sample consisted of women who were regularly menstruating and who, therefore, could be assumed to be undergoing regular hormonal fluxes. All of the women were on neuroleptics; none was taking contraceptive medications. Estrogen levels were not measured.

The symptom scale used was the Abbreviated Symptom Checklist (SCL-A) (McNiel and others 1989). This instrument had been previously used successfully for self-ratings by inpatients with schizophrenia. It has 34 items that can be divided into 6 symptom groups. The global score serves as a measure of general psychological distress. Ratings indicate the degree of distress on a 5-point scale. Subjects were first trained to use the scale and were subsequently sent home with a 1-month supply of daily checklists. They received a second 1-month supply when they returned for their monthly visit. In the interim, they were contacted by telephone once a week by the research assistant in order to monitor their adherence to the research task.

High and low estrogen phases were anchored to individual menstrual flow onset. The low estrogen phase was defined as the 5-day period which started on the 4th day of the menstrual cycle. The high estrogen phase was defined as the 5 days starting 12 days prior to onset of menstrual flow. The late luteal or premenstrual phase was not selected as the low estrogen phase for 2 reasons. First, subjects knew we were studying effects of the menstrual cycle and might be expected to attribute more symptoms to that time of the month. This has been seen in many studies of menstrual cycle pathology (Rubinow and Roy-Byrne 1984). Second, many women do experience an aggravation of mood symptoms in the late

luteal phase of their cycle, and we did not want that to contaminate the interpretation of our findings.

Analyses of variance (ANOVA) were performed for each of 6 symptom groups, as well as for the global score. There were, therefore, 7 ANOVAS, each consisting of 2 phases for 2 cycles for 5 subjects. Only the global score was significantly lower ($p < 0.05$) in the high estrogen phase than in the low estrogen phase, although all symptom cluster scores (depression, psychoticism, somatization, phobia, anxiety, hostility) were slightly lower in the high estrogen phase in all 10 menstrual cycles (Hallonquist and others 1993).

The Riecher-Rössler and others' study (1994) was based on a sample of 32 consecutively admitted women with schizophrenia (ICD-9 diagnosis using the PSE interview and the computer program CATEGO [Wing and others 1974]). Nine of the subjects were first admissions; the others suffered acute relapses of psychosis. They were followed during at least 1 cycle with hormonal levels taken on the 2nd, 7th, 13th, 14th, 21st, and 28th day of the cycle. The timing of the immunoassay was initially anchored to menstrual history and then to observed onset of menstrual flow. On the same days, a variety of clinician-, nurse-, and self-administered rating scales were used to assess psychopathology. The patients were not aware that menstrual correlations were the object of the study, and the raters were blind to the patients' cycles. Observed menstrual cycle length varied from 11 to 66 days, with an average of 28.4 days. All but 6 patients had taken neuroleptics in the week preceding admission and all were treated with neuroleptics and other psychopharmacologic agents, as needed, during the study period. All patients had markedly reduced estradiol levels throughout their cycle when compared to normative data.

Despite the confounding effects of neuroleptic treatment and the progressive improvement in symptoms found over the course of each subject's hospital stay, the authors demonstrated an estrogen effect on general psychiatric symptoms and, more specifically, on the thought disturbance subscore of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962). Less severe symptoms correlated with higher estrogen levels. More severe symptoms were associated with lower estrogen levels. Estrogen levels were cross-correlated with psychopathology scores for each subject separately. Mean values (except depression scores) all correlated in the expected direction. The thought disturbance subscore of the BPRS showed an inverse association with estrogen level that was significant at $p < 0.01$ (Riecher-Rössler and others 1994).

The Gattaz and others' sample (1994) consisted of 65 women aged 18 to 45 years with a DSM-III-R diagnosis of schizophrenia who were compared to 35 female patients with a DSM-III-R diagnosis of affective disorder. The age distribution of the 2 groups was similar. None of the patients was taking oral contraceptives, and women with irregular menstrual cycles were excluded. The subjects were divided into low and high estrogen phase admissions. The hypothesis was that the low estrogen phase admissions would have a superior treatment response as measured by neuroleptic dose requirement, by hospital duration, and by clinical status at discharge. The rationale was that, in this group, there was a specific hormonal trigger to relapse which should be relatively more responsive to standard treatment.

In both the schizophrenia and the affective sample, significantly more women were admitted during the low estrogen phase. This finding has been observed before and applies to all female psychiatric admissions, regardless of diagnosis (Luggin and others 1984). Women with schizophrenia who were admitted during the low estrogen phase required significantly lower mean daily doses of neuroleptics compared to those admitted during the high estrogen phase. They appeared to have a shorter length of hospital stay, but this was not statistically significant. Clinical state at discharge did not differ. Treatment-response comparisons were not made for the affective sample.

The authors acknowledge several limitations to the interpretation of this study, but speculate that if the dopaminergic disinhibition caused by decreased estrogen levels in the low estrogen admission group accounted for their relapse, then the increase in estrogen level as they moved through their menstrual cycle potentiated the effects of neuroleptics and permitted the effective therapeutic daily dose to remain relatively low.

DISCUSSION

Although the methodology was very different, the 3 studies suggest a modulating estrogen effect on symptoms in women with schizophrenia. While the Hallonquist and others' study (1993) assumed high and low estrogen phases, the Riecher-Rössler and others' study (1994) correlated actual estrogen determinations 6 times per cycle with psychopathology scores. It could be argued that an inpatient study is always confounded by the progressive overall improvement that takes place during the study period, especially since half of the subjects entered the hospital (and the study) during a low estrogen phase. The length of time before improvement and the length of cycles varied, however, and the authors did not feel that this issue interfered with the significance of their findings. The Gattaz and others' study (1994), in an indirect way, addressed this issue by showing that women admitted in the low estrogen phase improved at lower neuroleptic doses compared to those admitted during a high estrogen phase.

Because all patients in all 3 studies were being treated with neuroleptics, both estrogen fluctuations and symptom scores were dampened. This may have particularly affected psychotic symptoms, especially in the outpatient study. Nevertheless, psychopathology generally worsened when estrogen levels were low and improved when they were high. These results may not be specific to schizophrenia. They are, however, consistent with the clinical and epidemiological data

cited earlier, and they point to possible avenues for effective intervention.

These therapeutic possibilities of estrogens have been explored — but not often — in both men and women. Extrapyramidal symptoms and tardive dyskinesia (Bedard and others 1977; Nelson and others 1995; Villeneuve and others 1980) are known to improve when treated with estrogen compounds. Kulkarni and others (1995), in an open clinical trial, added estradiol to neuroleptics in the treatment of 11 women with acute psychosis and compared their course to that of 7 women treated by neuroleptics alone. The group receiving estrogens showed more rapid improvement but, by week 8 of the treatment, the 2 groups had attained similar levels of recovery. This preliminary work suggests that estradiol may facilitate neuroleptic responsiveness and could prove to be an important adjunctive treatment in the therapy of schizophrenia.

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