THE ROLE OF OESTROGENS IN SCHIZOPHRENIA[*]

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Introduction

As long ago as the beginning of the last century, psychiatrists recognized the possible association between schizophrenia and oestrogens (for review see 1). On the one hand, early clinicians such as Kraepelin (2) or Kretschmer (3) described signs of a *chronic* "hypooestrogenism" in women with schizophrenia. On the other hand, there have long existed observations indicating an association between oestrogen blood levels and *acute* psychotic symptomatology. Thus, acute psychosis seems to be ameliorated during physiological states such as pregnancy when oestrogen blood levels are high, but worsened during physiological states such as the postpartum period, the perimenstrual period, or menopause, when oestrogen blood levels are low.

The oestrogen protection hypothesis

Research of the last two decades has confirmed many of the historical observations concerning a protective effect of oestrogens in schizophrenia. And what is even more important, *basic research* has made important contributions to explain possible modes of action.

To begin with, identification of oestrogen receptors in the limbic system has led to the assumption that oestrogens not only play a role in the modulation of endocrine functions, but must also have a "neuromodulating function" (for review see 1). In the early 1980s, it was also observed that the effect of oestrogens in laboratory animals is in some respects similar to that of neuroleptics. It has also been shown that oestrogens can modulate the sensitivity and number of dopamine receptors. It was

therefore hypothized that oestrogens exert their antipsychotic effects similarly to traditional neuroleptics, mainly by blockade of dopaminergic transmission.

Today we know that oestrogens do not only modulate dopamine, but also serotonin, which is also thought to be relevant for schizophrenia and influence many other neurotransmitters and brain functions to such a degree that they have even been called "nature's psychoprotectant" (4).

In addition, *epidemiological* studies on sex differences in schizophrenic disorders suggest that the physiologically high estradiol production in young fertile women contributes to the later age of onset in women as compared to men and also to the better course of the disease, especially in young women. Thus, different epidemiological studies show that, in women, the disease, on average, begins four to five years later than in men. In own studies, we found peaks of illness onset at age 20 to 24 in men, but age 25 to 29 in women, and women also exhibited an additional smaller peak after age 45, i.e. when they start to loose their protection of oestrogens (5, 6).

Clinically, psychotic symptomatology has been shown to grow worse pre- or perimenstrually, -i.e. in the low oestrogen phase of the cycle (7). During pregnancy, when estradiol levels are 200 fold higher than normal, chronic psychoses seem to improve, but there is a 20 fold excess of psychosis after delivery, when oestrogen levels suddenly drop to normal. Furthermore, women with schizophrenia in the fertile age group of 20 to 40 years, i.e. the time of the highest ovarian estradiol production, need lower doses of neuroleptics than men of comparable age or older women - even when body weight is controlled. Finally, early puberty is associated with a later

onset of schizophrenia (for review see 1, 8). That means physiological oestrogens may play a role in delaying the outbreak of the disease.

In a *clinical study,* we examined 32 acutely admitted women with schizophrenia who gave a history of regular menstrual cycles. We saw a significant excess of admissions during the perimenstrual low oestrogen phase of the cycle, and, during the hospital stay of the 32 women, a significant association emerged between estradiol levels on one hand and different psychopathology scores on the other: psychopathology seemed to improve when estradiol levels rose, and vice versa (7). Interestingly, these patients showed many signs of a severely disturbed gonadal function with significantly lower estradiol and progesterone blood levels as compared to 29 controls with depressive disorders (9, 10).

Well in line with our findings, Hallonquist et al. (11) observed lower symptom scores in women with schizophrenia during the mid-luteal as compared to the early follicular phase of the menstrual cycle. They concluded that oestrogens may act as "endogenous neuroleptics".

Further interesting results come from our study on late-onset schizophrenia (12). In this study on a large representative population of 267 first admitted patients, we found that there are not only twice as many *women with onset over 40* as men, but they also suffer from a disease that is more severe as regards symptomatology and course as that of patients who fall ill early in life. One explanation for this could again be the loss of oestrogens.

Intervention studies are one of the best ways to test the oestrogen protection hypothesis. They have a very long tradition. As early as in the 1940s, Manfred Bleuer

(13) reported the first unsystematic trials using a combination of ovarian and pituitary hormones. Mall (14), a German psychiatrist in charge of a large hospital, examined 167 women suffering from schizophrenia with respect to oestrogen excretion in a 24-hour-urine sample, basal temperature, and vaginal cytology. Based on his findings, he divided the psychoses into two groups: hypofollicular and hyperfollicular. In the former group, he replaced oestrogens and found that "hypofollicular psychosis can be healed relatively easily by this substitution therapy". Unfortunately, Mall does not give many details about these interesting studies.

Several contemporary investigators have now reported promising results using oestrogen as a *therapeutic* agent. Kulkarni et al. (15, 16) found that schizophrenic women receiving estradiol as an adjunct to neuroleptic treatment show more rapid improvement in psychotic symptoms than women receiving neuroleptics alone (see Kulkarni et al., this issue). Similar effects were reported by Lindamer et al. (17) in a case report of a postmenopausal woman. Recently, Lindamer et al. (18) reported on a community sample of women with schizophrenia. Twenty-four women received hormone replacement therapy; twenty-eight women had never received such therapy. Interestingly, the users of HRT needed a relatively lower average dose of antipsychotic medication and suffered from less severe negative symptoms. Ahokas et al. (19) demonstrated positive effects of oestrogen substitution in two women with postpartum psychosis.

Implications for therapy and prophylaxis

Recent studies thus seem to confirm the observations of the early clinicians: Schizophrenic psychosis seem to be influenced by oestrogens. Further research into

this area seems urgent and also very promising, as new therapeutic strategies could emerge that would benefit the many women worldwide suffering from schizophrenia.

- One recommendation could be *hormonal replacement* with estradiol for women with schizophrenia *during perimenopause* as an augmentation strategy, an adjunct to neuroleptic medication. The dose of neuroleptics would be reduced and corresponding side effects minimized. To replace oestrogens in these women would at least attenuate perimenopausal complaints, which can contribute to a general deterioration of the mental state and, in vulnerable women, potentially provoke a psychotic episode. Oestrogen replacement therapy for women of this age group has been recommended for many reasons (20), but also seriously questioned recently, especially in its prophylactic use and in postmenopausal women of higher age groups (21-23). It has to be stressed in this connection, that there always should be an individual risk-benefit assessment. As for women with schizophrenia estradiol substitution could have additional benefits, further research on this potential *additional* indication is needed.

- *Research* should also be done *on the best mode of hormone replacement therapy* for psychiatric patients. If replacement consists of an oestrogen-progestogen combination, the progestogen can antagonize the positive effects of oestrogens with respect to mental state (24). Furthermore, we have to consider the risks of oestrogens as shown e.g. recently by the Women's Health Initiative Study (21-23), but also long-known risks such as endometrial and breast cancer. The newer synthetic steroids like tibolone seem to cause less endometrial proliferation. But their effects on the central nervous system are still not clear apart from the fact that they seem to have a mild androgenic effect and increase β-endorphin levels in the

pituary with improvement of mood and libido (25). Specific oestrogen receptor modulators (SERMS) of the second generation like raloxifene exert their main effect on bone.

- In women suffering from frequent perimenstrual psychotic *relapses "cycle-modulated" neuroleptic therapy* could be tried. However, this is a difficult regimen as regards compliance. Instead, especially if contraception is needed at the same time, *monophasic contraceptive pills could be taken continuously* (i.e. without intervals) in order to maintain a constant serum level of oestrogens (24). This requires a close cooperation between psychiatrists and gynaecologists and regular gynaecological visits.

- In any case, *oestrogens and the gonadal axis should in future be more seriously considered in the treatment of women with schizophrenia.* Psychiatric history taking should always include questions regarding menstrual irregularities, amenorrhoea, loss of libido, anorgasmia, infertility, galactorrhoea. If there are any clinical suggestions of oestrogen deficiency, prolactin and oestrogen levels should be tested.

- Hyperprolactinaemia can theoretically be caused by the disease itself and the accompanying stress, but also by neuroleptic treatment, and can lead to a secondary suppression of physiological oestrogen production. That means that many women with schizophrenia who take neuroleptics over years suffer from a partially *"iatrogenic premature menopause"* with all its potential short- and longterm consequences, as e.g. menopausal complaints or osteoporosis. In the case of hyperprolactinaemia with secondary oestrogen deficiency, atypical neuroleptics causing little or no hyperprolactinaemia (e.g. clozapine, quetiapine, aripiprazole or

olanzapine) are to be preferred. Otherwise oestrogens need to be added to the regimen.

- The question of *contraception* always needs to be taken into account. Thus, with the change to atypical neuroleptics which do not produce hyperprolactinaemia, the menstrual cycle is normalized and fertility is regained, with a high risk of unplanned pregnancy. Women with schizophrenia may not wish to be mothers and, as well, the new neuroleptics may have unknown teratogenic potential. Therefore, when changing to an atypical neuroleptic, contraception counselling involving a gynaecologist should be initiated.

- The *interaction of neuroleptics with oestrogen preparations* should always be considered. Thus, hormonal contraceptives can, for example, reduce metabolism of phenothiazine neuroleptics, which leads to an enhanced risk of side effects. On the other hand, certain neuroleptics can lead to reduced plasma levels of the contraceptive by hepatic enzyme induction, with the consequent risk of an unwanted pregnancy. This risk can be minimized by the continuous intake of a monophasic combined pill without a hormone free interval. Alternatively, an intrauterine device is a very reliable method of contraception.

Finally, it must be emphasized that many of the mentioned strategies are still being researched. Thus, regarding intervention studies, results of larger controlled studies are needed before recommendations for a broad clinical application can be made. Furthermore, as has been stressed already, the decision must always be made on the basis of an *individual* risk/benefit assessment (21-23). Certain strategies, however, should be part of current standard clinical care. These include questions

regarding the gonadal axis as part of routine history taking and a close co-operation with the gynaecologist in the therapy of women with schizophrenia.

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