Eur Arch Psychiatry Clin Neurosci (1993) 242:323–328

European Archives of Psychiatry and Clinical Neuroscience

Original Articles

Schizophrenia and Oestrogens – is There an Association?

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Received December 16, 1992

Summary. Some early psychiatrists already believed that schizophrenic disorders were associated with a disturbed balance of sexual hormones. This belief was based on the observation of a. an "insufficient functioning of the sexual glands" with so-called "hypoestrogenism", and b. an influence of ovarian function on schizophrenic psychoses. As this review shows, there are findings from recent research which seem to confirm that estrogens may have a protective effect in schizophrenia. There are also occasional hints at a possible "hypoestrogenism" in schizophrenia. In our own epidemiological, clinical and animal studies the hypothesis of a protective effect of oestrogens was for the first time systematically examined and confirmed. Oestrogens seem to modulate the sensitivity of D2-receptors in the brain, and clinically they seem to have a neuroleptic-like effect. These findings may have important implications for the prevention and therapy of schizophrenic disorders. Furthermore, our findings indicate the need to reinvestigate the question of a disturbed balance of sexual hormones in schizophrenic disorders. Further research on the role of oestrogens in schizophrenic disorders could in our opinion contribute to understanding the still unclear, possibly aetiologically heterogeneous pathogenetic mechanism of schizophrenic psychoses.

Key words: Schizophrenia – Oestrogens – Ovarian function – Menstrual cycle – Menopause

Introduction

Historical Background

From the time of early systematic observations on schizophrenia there have been observations and discussions on a possible association of this disorder with sexual hormones, particularly with oestrogens. Thus it was reported very early that many schizophrenic women suffer from oestrogen deficiency, at the time referred to as "hypoestrogenism". Further, it was noted that schizophrenic psychoses can be influenced by the natural variations of the oestrogen levels of a woman – both over the menstrual cycle and over the lifetime.

Already the early clinicians believed that schizophrenia is in part related to a disturbed balance of sexual hormones (e.g. Kraepelin 1909; Kretschmer 1921), as evidence had been found of a so-called "hypoestrogenism" and of "insufficient functioning of the sexual glands" (for reviews see Bleuler 1943; Diczfalusy and Lauritzen 1961). In 1921, Kretschmer wrote (p. 87): "In schizophrenics, one has always and with good reason paid special attention to these organs [the sexual glands]. Firstly, there is the fact that schizophrenic disorders have a marked preference for puberty.". Also (p.72): "Listing all cases of genital hypoplasia in schizophrenic women would appear useless, since such abnormalities are so frequent that almost the majority of all schizophrenic females would fall under this category.". He based his statements among other things on investigations of the "Fraenkel School", which in gynaecological examinations of several hundreds of schizophrenic women had found "considerable infantilistic changes of the genitals" in 70–80% of all cases, and on patho-anatomical examinations by Geller (1923), who had found in seven out of eight schizophrenic women "small ovaries with few follicles making a dead impression, small uteri with infantilistic proportions, small mucosal cells, narrow glands and a lack of cyclical proliferation" (cited according to Kretschmer, 1921, page 88–89).

Especially in the 1930s attempts were made to look into this question by performing estrogen analyses of the blood and urine. Diczfalusy and Lauritzen (1961) give an overview of the respective studies published between 1933 and 1955: Seven studies showed decreased blood levels of oestrogens. Only one author reported increased values. The findings, however, were mostly based on small numbers of patients and on biological methods only. Baruk et al. (1950) examined vaginal smears for estrogen influence. They found "hypoestrogenism" in 23 cases of "Dementia praecox". These early findings are of special interest, as until the 1950s there was no neuroleptic therapy, i.e. the observed abnormalities could not be attributed to neuroleptics.

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In the older literature there are not only reports on evidence for a general "hypoestrogenism" in schizophrenic females, but also several hints that oestrogens might influence schizophrenic disorders: Thus, as early as the last century Kraft-Ebbing (1896) was among the first to notice that some women became psychotic mainly before or during menstruation, i.e. during the time of the female cycle when the usually high oestradiol blood levels of women are markedly reduced. This had even lead to a separate diagnostic category, the "menstrual psychosis" (Kraepelin, 1909). Kretschmer (1921) reported cases with the outbreak of schizophrenia in temporal relation with "surgery of ovaries, pregnancy, delivery and puerperium", i.e. also in association with a marked change, mainly a decrease, of the oestrogen blood level. Finally, it was noted that late onset schizophrenia, i.e. schizophrenic disorders with onset after age 40–45 years, are much more frequent in females than in males. Already Bleuler (1943) associated this with the "loss of ovarian functioning" starting at the same age.

Based on the observed "hypoestrogenism" on the one hand and the susceptibility of schizophrenic psychoses by oestrogens on the other, first substitution trials using a "combined ovarian anterior pituitary hormone" were undertaken, which were unsystematic at first (Bleuler, 1943). Only later did Mall (1959, 1960) examine a larger sample comprising 167 schizophrenic females admitted to a state mental hospital with regard to their oestrogen excretion in 24-h-urine, their basal temperature and vaginal cytology. He concluded that there are two different forms of psychosis, a "hypofollicular" and a "hyperfollicular" one. In the former he substituted oestrogens using Primodian or Depot Progynon and found that "... hypofollicular psychoses can be healed relatively easily with this substitution therapy" (Mall 1959, 1960). Unfortunately, Mall gives very little detail of his study. Thus he does not, for example state how "healing" was defined, not to mention the insufficient reliability of diagnoses at that time.

Taken together, it can be stated that research strategies and methodology in this area were quite inadequate until the middle of this century. The findings were forgotten or at least not further investigated. Nevertheless, two hypotheses can be derived from these early observations:

1. The hypothesis of "hypoestrogenism" in schizophrenic females: schizophrenic disorders are associated with a chronic oestrogen deficiency syndrome – at least in a subgroup of females. To quote Kretschmer 1921 (p. 89): The overall impression that remains when overviewing all clinical and morphological facts reported, is that the material concerning the gonads is incriminating from many sides at least for some of the schizophrenic cases. And especially in the direction of a hypo- or dysfunction.

2. The hypothesis of a protective effect of oestrogens in schizophrenic disorders: Young females in comparison with males seem to be relatively protected from the outbreak of the disease by their comparatively very high physiological oestrogen production. They mainly seem to fall ill when their oestrogen blood level drops drastically – be it in the course of the menstrual cycle before and during menstruation, or in the course of the lifetime before and during menopause, or associated with other causes of a drastic drop of oestrogen levels. And: oestrogen substitution therapy seems to be valuable in some cases of schizophrenic psychoses.

Recent Studies

Until recently there had been no study which had investigated these hypotheses systematically. In the meantime, however, basic and experimental as well as clinical and epidemiological research provides quite a number of single findings, which are interesting in this connection.

As regards the hypothesis of "hypoestrogenism", the oestrogen balance of schizophrenics has not been directly investigated up to now. There have, however, been some studies on the gonadotrophins FSH (follicle stimulating hormone) and LH (luteinising hormone), which play a role in regulating the ovarian oestradiol production (oestradiol is the main component of estrogens in fertile, nonpregnant women). In chronic schizophrenics one can find decreased serum levels of FSH and LH as compared with controls (Brambilla et al. 1975; Brambilla 1980; Kane et al. 1981; Ferrier et al. 1983). In these cases a decreased oestrogen production is to be expected as well. Prentice and Deakin (1992) found in 18 of 42 patients of a neuroleptic depot clinic irregular cycles, which were independent of the neuroleptic dosage according to their findings (see below). Oestrogens were not, however, analysed by any of these researchers.

In contrast to the hypothesis of hypoestrogenism, one can find much more evidence for the hypothesis of a protective effect of oestrogens from recent research. In the meantime there are even hints on the possible mode of action: oestrogens seem to influence the dopaminergic system in the brain and to have at the same time a clinical effect similar to that of neuroleptics. This means, that oestrogens could play a role within the dopamine hypothesis of schizophrenia. According to this hypothesis there is an increased dopaminergic activity in the brains of schizophrenics (Carlsson 1987). Even if the evidence for the validity of this hypothesis is not yet conclusive (Gattaz et al., 1983; Carlsson, 1987), schizophrenic symptoms (at least the productive ones) can nevertheless be successfully treated and suppressed with substances which diminish the dopaminergic activity in the brain. Such substances are neuroleptics and possibly oestrogens as well.

Thus, in the early 1980s it was observed that the effect of oestrogens in laboratory animals is quite similar to that of neuroleptics. They can for example enhance neuroleptic induced catalepsy (Gordon et al. 1980; DiPaolo et al. 1981; Nicoletti et al. 1983) and reduce amphetamine and apomorphine induced behavioural changes such as stereotypies (Gordon et al. 1980; Hruska and Silbergeld 1980). This lead to the conclusion that oestrogens have – just as neuroleptics – antidopaminergic properties. It was also shown that estrogens can reduce the dopamine concentration in the striatum (Foreman and Porter 1980; Dupont et al. 1981) and modulate the sensitivity and number of dopamine receptors (Koller et al. 1980; Gordon and Diamond 1981; Bédard et al. 1984). Finally, the identification

of oestrogen receptors in the limbic system further supported the assumption that oestrogens not only play a role in the modulation of endocrine functions, but also have a "neuro-modulating function" (Holsboer et al. 1983; Lobo et al. 1984; Maggi and Perez 1985).

Clinically now as before there are only case reports on women whose psychotic symptomatology was exacerbated pre- or perimenstrually, i.e. in the low oestrogen phase of the cycle (Endo et al. 1978; Glick and Stewart 1980). During pregnancy, a time with extremely high oestrogen levels, chronic psychoses seem to improve (Chang and Renshaw 1986). After delivery, however, when the estradiol level suddenly drops, an enhanced vulnerability for psychoses was observed (Nott 1982; Kendell et al. 1987). These "puerperal psychoses" could be triggered by the oestrogen fall after delivery, as the drop can possibly cause hypersensitivity of dopamine D_2-receptors (Cookson 1981; Wieck 1989).

Furthermore, it was noted that schizophrenic females in the fertile age group 20–40 years, i.e. during the time with the highest ovarian oestradiol production, need less neuroleptics than older females or males of the same age group – even controlled for body weight (Seeman 1983; Hogarty et al. 1974; Goldstein et al. 1978). At the same time oestrogens seem to have a positive effect on neuroleptic-induced dyskinesia, which also points at their having antidopaminergic properties (Bédard et al. 1977; Villeneuve 1980).

Finally, certain sex differences in schizophrenia, well established by epidemiological studies, could be explained by the hypothetical protective effect of female sex hormones, hence the later age at onset of females as compared with males and the presumably better course of the disease in the former. In this context, Häfner (1987) has formulated the hypothesis that oestrogens delay the outbreak of the disease in females by enhancing the vulnerability threshold. Also other authors such as Lewine (1988), Seeman (1981, 1983) and Seeman and Lang (1990) have again taken up the estrogen hypothesis in this connection.

Häfner has now for the first time initiated a systematic testing of the oestrogen hypothesis in schizophrenics. In a stepwise proceeding the reported epidemiological and experimental findings were reanalysed with sound methodology and further investigated. At the same time the hypothesis of a protective effect of oestrogens in humans was tested in a clinical study.

Own Studies

Epidemiological Studies

In the framework of the *ABC*-Schizophrenia-Study, an epidemiological investigation of the influence of *a*ge and sex factors in this disease as well as its *b*egin and *c*ourse, we have systematically examined among other things the age at onset and at first admission in schizophrenic disorders (Häfner et al. 1989, 1991a, c; Riecher et al. 1989, 1991). In different populations – in representative case register samples from Denmark ($n = 1.169$) and Mannheim ($n = 335$) as well as in a directly examined representative population of first admitted patients in the Rhine-Neckar-District (ABC-sample, $n = 392$) – we could show that at first admission for a schizophrenic disorder females were usually 3–4 years older than males. Furthermore, we could demonstrate that this age difference did not exist at first admission only, but also at true onset.

Another observation was of special interest: in all populations examined females, apart from their delayed peak of onset in the younger age group (in the age group 20–24 years in males, but in the age group 25–29 years and markedly flatter in females) also had a second, smaller peak of onset after age 44 years, i.e. around premenopause and menopause. This result again pointed to the possible influence of oestrogens: ovarian estradiol production in females is at its maximum from puberty until premenopause, which nowadays usually starts around age 45 years in Western countries. So if the hypothesis was true that oestrogens enhance the vulnerability threshold for schizophrenia (Häfner 1987), young females would be protected from the outbreak of schizophrenia to a certain extent. The outbreak of the disease would be postponed by this protective factor. This would explain why young females have a flatter and delayed peak of onsets as compared with males. With the decreasing oestradiol production during premenopause and menopause, this protective factor would rapidly decline and females would "catch up" in their morbidity risk. This could explain the second peak of onsets after age 44.

Animal Experiments

In a next step of systematic testing, animal experiments were undertaken in order to further clarify the neurohormonal mechanisms of oestradiol action (Häfner et al. 1991a–c; Gattaz et al. 1991). An experimental model was used in which the effects of the hormone on behavioural changes induced by the dopamine-antagonist haloperidol (catalepsy) and by the dopamine-agonist apomorphine (oral stereotypies, grooming and sitting behaviour) were investigated in neonatal and adult treated rats. Oestradiol significantly reduced the behavioural changes induced by both haloperidol and apormorphine, and this effect was more pronounced in neonatally treated animals. The latter could be a hint at a structural effect of physiological oestradiol concentrations on the dopaminergic system during pre- and perinatal development of the brain. Although this early effect of oestradiol seemed to be the stronger one, there was no doubt about a "functional" dopamine antagonising effect of oestradiol in the adult brain at the same time. An additional finding was a reduction of the dopamine receptor affinity for sulpiride, which implies that oestradiol reduces the D2-receptor sensitivity in the brain (Häfner et al. 1991a, b; Gattaz et al. 1991).

Clinical Study

In a further step we analysed the functional effects of oestradiol in human beings using the female menstrual cycle as a model. In this clinical study we tested the hypothesis that the symptomatology of schizophrenic females

varies during the menstrual cycle, depending on the fluctuations of the oestradiol blood level (Riecher-Rössler et al. 1993). We examined 32 acutely admitted female schizophrenics (PSE/Catego diagnoses according to ICD-9), aged 18–43 years (mean 30.5), who gave a history of regular menstrual cycles. The patients were examined on admission and at defined days of their cycle, while each time analysing their estradiol serum level and different other hormonal parameters as well as their psychopathology. The latter was assessed using different self and expert rating scales.

We found a significant excess of admissions during the perimenstrual, i.e. the low oestrogen phase of the cycle, as compared with the high oestrogen phase ($P \leq 0.01$), which can be seen as a first, indirect hint at an effect of oestrogens. In a direct testing of the association between symptomatology scores and estradiol level during hospital stay, we could demonstrate highly significant inverse associations: symptoms deteriorated with falling oestradiol levels and vice versa. This was true for psychiatric symptoms as assessed by the psychiatrist ($P \leq 0.01$), for behaviour on ward as assessed by the staff ($P \leq 0.01$), as well as for "paranoid tendencies" and "general well-being" as assessed by the patients themselves ($P \leq 0.05$). Only "depression" did not show such an association, which was in line with the expected neuroleptic-like clinical effect of oestrogens.

At the same time the study revealed some interesting findings concerning the hypoestrogenism hypothesis: all 32 patients examined suffered from a marked gonadal dysfunction. This was so, although they represented a "positive" selection of schizophrenic patients, for we had in our study only included females who gave a history of regular cycles. The serum levels of prolactin, oestradiol and progesterone measured during the cycle indicated an ovulatory cycle in only 14 of the 32 patients. And five of these 14 seemed to suffer from corpus luteum insufficiency. All patients – even those with ovulatory cycles – showed a markedly reduced ovarian oestradiol production as compared with the normal population, with oestradiol levels fluctuating only very slightly during the cycle (Riecher-Rössler et al. 1993).

Discussion

Recent studies, not least our own, seem to confirm the observations of the early clinicians: the female sexual hormones, the oestrogens, appear to play some role in schizophrenic psychoses. On the one hand there again occurred occasional hints at a possible estrogen deficiency syndrome in schizophrenic females, while on the other hand, there were numerous and far more substantial hints at the susceptibility of schizophrenic psychoses by oestrogens.

As to the suspected hypoestrogenism of schizophrenic females, this phenomenon, to our knowledge, has not further been investigated since the 1950s. The only more recent findings of limited interest in this connection are the decreased gonadotrophine levels and the excess of cyclic irregularities in schizophrenics. In our own clinical study we could show that most acutely admitted schizophrenic females of a psychiatric hospital suffer from gonadal dysfunction. Although those patients who gave a history of irregular cycles had been excluded from the study at the beginning, almost all patients showed a disturbed gonadal function with decreased oestradiol production.

As all our patients were treated with neuroleptics, this could potentially be caused by neuroleptic-induced hyperprolactinaemia, (prolactin can suppress ovarian oestradiol production (Diedrich and Wildt 1990)) yet to date such relationships have never been examined in schizophrenic women. Only Prentice and Deakin (1992) presented preliminary results on this in their study already mentioned. 18 of the 40 patients examined by them suffered from irregular cycles. Concerning neuroleptic dosage and prolactin serum levels they did not find a difference between the group of patients with regular and that with irregular cycles. They concluded from this that menstrual irregularities are probably not – or at least not mainly – caused by neuroleptics. For male schizophrenics, Brambilla (1975) showed that the oestrogen excretion in the urine, which was in the normal range before treatment, even *in*creased in one-third of the patients when treated with the neuroleptic haloperidol. In our opinion, however, this result is not directly transferable to female schizophrenics. As to the influence of neuroleptics on the gonadotrophins FSH and LH, the results are contradictory (Brambilla et al. 1975; Collu et al. 1977; Czernik and Kleesiek 1979; Beumont et al. 1974; Naber et al. 1980). Finally, there is still the fact that signs of a gonadal dysfunction or hypofunction and hypoestrogenism have been observed long before the introduction of neuroleptics. This also implies that the disturbances are not due solely to neuroleptics.

As to the question of a gonadal dysfunction and its possible role in schizophrenic disorders, it seems therefore worthwhile to retest the observations and findings of the past with today's sophisticated methods in untreated neuroleptic-naive schizophrenics. If the findings could be confirmed, the question of course would remain whether they are part of the pathogenetic process itself or rather a secondary reaction to it, i.e. a reaction of the endocrine system to general "stress".

As to the susceptibility of schizophrenic psychoses by oestrogens, the findings are much clearer: the epidemiological findings as well as the results from basic and experimental research and finally our clinical findings indicate that oestrogens can act as a protective factor in schizophrenia. The fact that apart from a delay of the onset of the disease in females we also found a second peak before and at menopause seems to confirm the hypothesis formulated by Häfner (1987), as such a distribution of onsets over the different age groups rather exactly mirrors the distribution of oestradiol levels in females over the lifetime.

The results of our clinical study furthermore show that the protective effect of oestrogens varies with their serum level not only over the lifetime but also in the course of each menstrual cycle, i.e. *if* there is a psychotic outbreak or relapse, it obviously occurs mainly in the low oestrogen phase of a cycle.

The clinical effect of oestradiol seems to be similar to that of neuroleptics, as we could observe not only a gen-

erally stabilising, but also an antipsychotic effect. Our clinical study therefore supports the findings from our animal experiments, which indicated that oestradiol can reduce dopamine-D_2-receptor-sensitivity (Häfner et al. 1991a–c). The clinical study goes beyond the animal study as it shows an effect of oestrogens also in humans. It also goes beyond the epidemiological study, which had only indicated an influence of oestrogens on the age at first onset and therefore on the vulnerability threshold for the outbreak of the disease: the clinical study also implies an influence of oestradiol on the intensity of symptoms.

Taken together, the findings reported do by no means imply an aetiological role of oestrogens in the disease process. Kretschmer (1921) wrote (p. 89): "Bearing all this in mind, one will have to be careful not to visualize the possible aetiological involvement of the gonads in schizophrenic disorders as a simple, massive, monosymptomatic functional loss... Assuming an endocrinological aetiology (co-aetiology, respectively) to be probable, one will have to think of this only in the form of a very complicated constitutional syndrome, an interlocked chemical relation between brain and combines of glands with an especially strong aetiological predominance of the gonads. The brain as the effector organ of all these effects must never be neglected then, so that we do not fall back from neuro-anatomical to endocrine-chemical one-sidedness".

At present, unfortunately, we hardly know more about the aetiology of schizophrenia – or rather of schizophrenic disorders – than did Kretschmer 70 years ago. Neither do we know of unequivocal cerebro-anatomical changes – although mainly based on findings from modern neuroimaging techniques such abnormalities are still debated – nor have we learned a lot more about the endocrine side. The only well-proven knowledge to date is that substances which block the neurotransmitter dopamine, i.e. act as "antidopaminergic" agents, have antipsychotic properties and can suppress schizophrenic symptomatology. As regards a possible interaction between structural cerebral and endocrine changes, Prentice and Deakin (1992) found in their sample that patients with irregular cycles suffered from markedly severer schizophrenic symptoms – concerning positive as well as negative symptoms – than patients with regular cycles. And there were also more pronounced hints at organic brain disease in the former group. They concluded from this that the irregular cycles could be due to structural cerebral changes. However, such a simple explanation in our opinion runs the risk of falling back into "neuro-anatomical one-sidedness". In fact, nowadays explanations seem much more likely which take into consideration the complex interactions between neurotransmitter systems, neuroanatomy, neuroendocrinology and last but not least psychological effects. Where in the "feedback mechanism" psyche – neurotransmitter system – neuroendocrinology and its neuroanatomical substrates lies the cause of the disturbance, continues to be one of the big mysteries of psychiatry. In our opinion, the oestrogens could, however, be a helpful "window" giving more insight into the pathogenesis of schizophrenic syndromes.

Furthermore, oestrogens – if their protective effect could be confirmed – could have an immediate clinical relevance for therapy and relapse prevention of schizophrenic disorders. Firstly, in young, schizophrenic women, one could consider the adjustment of the neuroleptic dose to the menstrual cycle, i.e. to give higher doses premenstrually and during menstruation as opposed to lower mid-cycle doses. Thus, some perimenstrual exacerbations might be avoided, or we could achieve the same therapeutic and relapse-preventing effect with a lower overall neuroleptic dose, which would have the advantage of fewer side-effects. Secondly, women in or after menopause could undergo a hormonal substitution therapy, similar to that used against ostereoporosis. Corresponding intervention studies should be carried out in a next step. Hopefully, in the long run such a "cycle-modulated" neuroleptic dosage in young women on the one hand and an "adjuvant" oestrogen therapy in menopausal and postmenopaual women on the other could – at least in women – have a positive influence on the course of schizophrenic disorders.

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