
Psychotic Disorders and Menopause: The Untold Story

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Abstract

This chapter aims to give an overview on the influence of menopause on psychotic disorders. Menopause is associated with a loss of estrogens; estrogen has important neuro- and psychoprotective activities, thus its decline and/or instability may trigger or aggravate mental disorders including psychotic ones. As a result, perimenopause may lead to an enhanced risk of first onset of schizophrenic psychoses or 'late-onset schizophrenia'. Women with pre-existing chronic schizophrenia tend to have a deterioration of their illness after menopause and a higher demand for antipsychotic medication. Apart from the psychotic symptoms, many other conditions can be aggravated by the loss of estrogens, including sleep disturbances, irritability, depression, cognitive impairment and sexual problems. In addition, many females with diagnosis of schizophrenia may present with premature menopause due to antipsychotic or stress-induced hyperprolactinemia and the subsequent gonadal suppression. Apart from psychotherapy and social measures, replacement of 17 β -estradiol may be helpful in women with schizophrenia in the perimenopause and early postmenopause, but its use might also carry some risks. More research is needed on the indications and contraindications for hormone replacement in this context.

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Approximately 100 years ago, the age of menopause in our society often exceeded women's life expectancy, with the result that many women did not experience the medical problems nowadays associated with the menopause. Today the average life expectancy of a female in our society exceeds 80 years and, consequently, women now live more than one third of their lives during the postmenopause.

In addition to the obvious physical changes occurring around the menopause, this phase of life is often burdened with numerous emotional stressors that have already been explored in other chapters of this book.

The sudden loss of estrogen activity may also have a negative impact on mental functioning. There is an increasing body of evidence from basic science, epidemiological data and interventional studies to indicate that estrogens play a role in

positively influencing mental well-being [1, 2, for review]. From the clinical point of view, depressive symptoms and even an upsurge in the incidence of some severe mental disorders, such as schizophrenia [3], have been observed around the menopause, suggesting direct involvement of the estrogen activity.

Methodological Problems

Research on the relationship between menopause and mental health shows some difficulties and methodological limitations, which are briefly described here.

First, 'menopause' is often not clearly defined and not well differentiated from 'perimenopause' and 'postmenopause', even menopause is sometimes not differentiated from natural surgical menopause. Furthermore, many studies have relied on self-reporting of women and did not include measurements of hormonal serum levels. Fourth, studies were quite often based on clinical samples rather than community-based cohorts. Fifth, many studies have only examined the occurrence of mental disorders cross-sectionally and not through longitudinal assessment of well-established cohorts.

Finally, the extent to which the menopause itself affects psychological symptoms is of difficult interpretation, particularly given the fact that the normal aging and the menopausal transition share common biological and psychosocial characteristics.

Role of Estrogens in Schizophrenic Psychoses

Estrogens: A Protective Factor in Schizophrenia?

Historical Findings

Since the last century, psychiatrists have been able to recognize the possible association between schizophrenia and estrogens (for review, see [4]). On the one hand, early clinicians such as Kraepelin and Kretschmer described signs of *chronic* 'hypo-estrogenism' in women with schizophrenia. On the other hand, there have been observations on the association between estrogen levels and *acute* psychotic symptomatology. Kraft-Ebing was among the first to describe women becoming psychotic before or during menstruation, i.e. when estrogen levels are relatively low. Kraepelin even created a separate diagnostic category, labelled 'menstrual psychosis'. Kretschmer reported cases where the outbreak of schizophrenia had a temporal relationship with 'surgery of ovaries, pregnancy, delivery and puerperium'. Finally, Manfred Bleuler noted that late-onset schizophrenia (with onset after age 40 years) was much more frequent in women than in men, a finding he attributed to the 'loss of ovarian function' starting at around that age [4].

Basic Research Findings

Important findings from basic research revealed estrogen receptors in the limbic system of the brain, and the observation that the effects of estrogens in rodents are, in some respects, similar to those of neuroleptics. Furthermore, it was shown that estrogens can modulate the sensitivity and number of dopamine receptors. It was therefore hypothesized that estrogens exert their antipsychotic effects in a manner similar to that of traditional neuroleptics, at least partly via blockade of dopaminergic transmission [4].

In addition, it has been documented that estrogens, and especially 17 β -estradiol (the natural estrogen that is most active in the brain), produce many other neuroprotective and psychoprotective effects. For example, estrogens appear to improve cerebral blood flow and glucose metabolism, promote neuronal sprouting and myelination, enhance synaptic density and plasticity, facilitate neuronal connectivity, act as antioxidants, and inhibit neuronal cell death. Estrogens also exert profound effects on brain differentiation during development, particularly during late gestation and during the early postnatal period, and are important in normal maintenance of brain function during aging [2].

The mechanism of action of estrogens depends not only on the classical genomic pathway, but also involves nongenomic, rapid interactions, which explains the differing latency of effects. Estrogens clearly modulate the dopaminergic and other neurotransmitter systems that are believed to be relevant to schizophrenia, such as the serotonergic and glutamergic system, but also the noradrenergic and cholinergic system [2]. Recently, it has even been suggested that 17 β -estradiol in the brain might rather be regarded as a neurotransmitter itself than as a hormone [5].

There are at least two subtypes of estrogen receptors, namely estrogen receptor- α and estrogen receptor- β , which are transcribed from two distinct genes. Autopsy studies showed that estrogen receptor- α messenger RNA is expressed in discrete areas of the human brain such as amygdala, hypothalamus, cerebral cortex and hippocampus; these areas are associated with neuroendocrine function, as well as emotion, memory and cognition [2].

Epidemiological and Clinical Findings

Epidemiological studies of sex differences in schizophrenic disorders suggest that high estradiol production in young fertile women may contribute to the later age of onset in women compared to men, and to a better course of the disease especially in young women. Various epidemiological studies show that among females the disease on average begins 4–5 years later than in men (age 20–24 in men, 25–29 in women) [3], interestingly, women also exhibit an additional peak after age 45. Therefore, it has been postulated that estrogens raise the vulnerability threshold for the outbreak of the disease [4]. According to this hypothesis, women are, to some degree, protected against schizophrenia between puberty and the menopause by their relatively high gonadal estrogen production during this period of time. Women would lose the protection

of estrogens with the onset of estrogen fluctuations/decline, which could account for their second peak of illness onset after age 45. Clinically, psychotic symptomatology has been shown to increase pre- or perimenstrually, i.e. in the low estrogen phase of the cycle [1, 2]. We examined 32 acutely admitted women with schizophrenia with history of regular menstrual cycles, and observed an increase in admissions during the perimenstrual low estrogen phase of the cycle. Furthermore, during the admission of these patients, a significant association emerged between estradiol levels and psychiatric symptomatology: symptoms appeared to improve when estradiol levels rose, and vice versa [6].

Seeman [7] noted that women with schizophrenia in the fertile age group of 20–40 years need lower doses of neuroleptics than do men of comparable age or older women, even when body weight is controlled. Gattaz et al. [8] in a further study found evidence of a differential therapeutic response depending on the phase of the menstrual cycle.

During pregnancy when estrogen levels are about 200-fold higher than normal, chronic psychoses seem to improve, but there is a 20-fold excess of psychosis after delivery, when estrogen levels suddenly drop to normal [1, 2]. Psychoses associated with other forms of estrogen withdrawal such as after abortion, removal of a hydatiform mole, cessation of oral contraceptives, clomifene and tamoxifen administration (both estrogen receptor antagonists) and gonadorelin agonist administration (blocking pituitary stimulation of endogenous estrogen secretion) have also been described [9].

Menopause and Schizophrenia

In a study of a large representative population of 392 first-admitted patients [10], we were able to show that the incidence of schizophrenia in the age group 40–60 years was about double in women, compared with men. First admission for schizophrenia after age 40 occurred in only 10% of all men with schizophrenia, but in about 21% of all women with this diagnosis. The yearly incidence rate in women over age 40 was 8.9 per 100,000, whereas it was only 4.2 per 100,000 in men [10] (fig. 1).

Interesting findings have been reported with respect to symptomatology and disease course of these late-onset women: *Men with onset over age 40* show significantly milder symptoms and spend less time in hospital than do early-onset patients, whereas late-onset women suffer from a disease that is almost as severe as that of patients who fall ill early in life [10]. An explanation for this could again be the estrogen effects: if onset of illness in women with a relative high vulnerability is delayed by estrogens, this high vulnerability is ‘unmasked’ by the loss of this estrogen protection around the time of the menopause. These women therefore are not only more frequently represented in the late-onset group but also have more severe symptoms and a worse course of illness. In addition, the depletion of dopamine receptors with age seems to be more precipitous in men than in women.

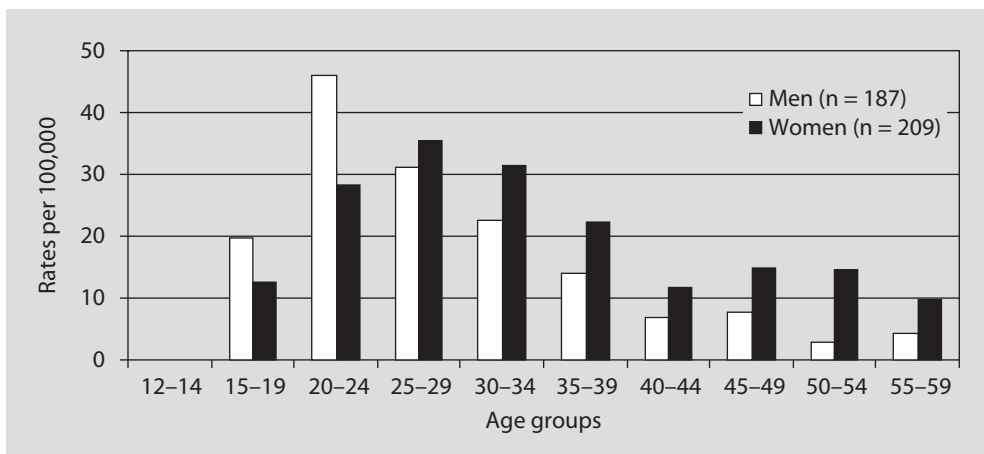


Fig. 1. Sex-specific age-distribution of first admissions because of schizophrenia and paranoid psychosis. From Häfner et al. [3].

Well in line with this are the results of long-term schizophrenia studies which have shown that the course of schizophrenia in women tends to deteriorate during the peri- and postmenopause [1, 2].

Intervention Studies with Estrogens

Intervention studies with estrogens have been conducted in women with schizophrenia of all age groups. As early as the 1940s, Bleuler [11] reported the first unsystematic trials using a combination of ovarian and pituitary hormones. Mall [12], a German psychiatrist in charge of a large hospital, examined 167 women suffering from schizophrenia with respect to estrogen 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 estrogens and found that ‘hypofollicular psychosis can be healed relatively easily by this substitution therapy’.

Also, several contemporary investigators have now reported promising results using estrogen as a therapeutic agent. Ahokas et al. [13] demonstrated positive effects of estrogen substitution in two women with postpartum psychosis, and Sichel et al. [14] noted a prophylactic effect concerning this disorder. In a Cochrane review in 2005, Chua et al. [15] could only find five randomized double-blind intervention studies with a satisfying methodology, with most studies showing weak or nonsignificant effects. However, most of these studies employed conjugated estrogens rather than 17β -estradiol – the latter show to have pivotal activity in the brain. Furthermore, in order to prevent endometrial hyperplasia, the estrogens were usually combined with progestogens which can counteract the positive effects of estradiol in the brain.

Kulkarni et al. [16] found that schizophrenic women receiving estradiol as an adjunct to neuroleptic treatment showed more rapid improvement in psychotic symptoms than women receiving neuroleptics alone. In a recent randomized, double-blind study, the same group [17] showed that adjunctive transdermal estradiol significantly reduced positive and general psychopathological symptoms.

Most studies were conducted in young, premenopausal women. Only Good et al. [18] examined *postmenopausal* patients. He administered estradiol and progesterone to 14 women with schizophrenia, schizophreniform or schizoaffective disorder and found a significant improvement of negative symptoms within six months. There are also some case reports regarding positive results of HRT in postmenopausal women with schizophrenia. Bergemann et al. [19] reported a case of a woman with first onset of schizophrenia in the perimenopause. She experienced severe first-rank symptoms over several months, but refused antipsychotic treatment. As she was symptomatic and believed to be in the perimenopause, therapy with transdermal estradiol in combination with norethisterone acetate was initiated and led to an impressive remission of the psychotic symptoms.

Lindamer et al. [20] reported on a postmenopausal woman whose psychotic symptoms improved on estradiol as an adjunct to her antipsychotic therapy. In 2001, Lindamer et al. [21] studied a community sample of postmenopausal women with schizophrenia. Twenty-four women received hormone replacement therapy (HRT), 28 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.

Premature Menopause in Schizophrenia

Several studies suggested disturbances in the gonadal function and hypoestrogenism in younger women with schizophrenic psychoses, similar to a 'premature menopause' [1]. Menstrual irregularities and reduced estradiol, progesterone and gonadotropin (FSH, LH) blood levels throughout the menstrual cycle, as well as anovulation and reduced fertility are also reported.

In our own study of 32 acutely admitted schizophrenic women, there was a greater variation in cycle length and significantly lower estradiol and progesterone blood levels throughout their menstrual cycle compared with 29 controls. Fifty-six percent presumably suffered from anovulation, which is a much higher proportion than in the control patients where anovulation was suspected in only 19% [22].

These findings are probably a consequence of neuroleptic-induced hyperprolactinemia which is known to suppress gonadal function [23]. As hypoestrogenism was also observed before the introduction of neuroleptics, it is possible that also 'stress' associated with psychosis could induce hyperprolactinemia and the respective gonadal suppression.

Estrogens and Bipolar Disorder

Little is known about the impact of female reproductive hormones on the course of bipolar disorder. Freeman et al. [24] assessed 50 women with DSM-IV bipolar disorder with a structured clinical interview regarding the impact of reproductive events on the course of the illness. They found an increased risk of mood symptoms at times of reproductive events. 2/3 of the women with children experienced a postpartum mood episode (mainly depressive episode). 22 of the women were currently either peri- or postmenopausal. Twelve of these women reported worsening of mood, namely an increase in depressive symptoms, increased irritability, hypomania or mania and more frequent cycling. Women who were not using hormone replacement therapy (HRT) were significantly more likely to report worsening of symptoms during perimenopause/menopause than those who were using HRT.

Estrogens' Influence on 'Accompanying' Symptoms of Psychosis

Physiological estrogens as well as HRT might have further positive effects in the therapy of psychosis. Thus, they might have stress-protective properties and thereby buffer against relapses. Furthermore they seem to have positive effects on cognition which is important, since minor cognitive deficits are often one of the main obstacles for rehabilitation in the post-acute phase of the disease. Again, cognitive properties of estrogens appear to be more associated with 17 β -estradiol rather than CEE (conjugated equine estrogens) [25, 26].

Hormone Replacement Therapy?

Trials should be initiated on therapy with estrogens for women with schizophrenia *during and after the perimenopause* as an augmentation strategy to neuroleptic medication. Possibly, the dose of neuroleptics could then be reduced and the corresponding side effects minimized. Estrogen therapy could also attenuate perimenopausal complaints such as hot flushes, night sweats with sleep disturbances and general irritability (table 1), symptoms that could lead to general deterioration of the mental state and potentially provoke a psychotic episode. Nonetheless, it has been reported that women with schizophrenia are less likely to ever use HRT as compared to women without psychiatric diagnosis [27]. Further research on the benefits of HRT for schizophrenic patients is therefore overdue.

Some of the positive effects of estrogens have been questioned in the context of perimenopausal estrogen replacement by studies such as the WHI, Women's Health Initiative Study [29], the WHI-M, Women's Health Initiative Memory Study [25] or the HERS, Heart and Estrogen/Progestin Replacement Study [30]. However, the

Table 1. Some important effects of estrogen replacement [28, 31, 32]

Positive	Negative
Perimenopausal complaints ↓ Physical: hot flushes, genital discomfort, aging of collagen (skin, joints, intervertebral discs) Mental: depression, irritability, emotional lability ↓	Endometrial carcinoma ↑ if unopposed estrogens are administered (→ in women without hysterectomy always combine with progestogens!)
Risk of osteoporosis ↓	Risk of breast cancer ↑? (→ not in patients with a familiar or own risk and usually not longer than 7 years!)
Delay of cognitive decline/Alzheimer?	Risk of thrombosis and cerebral insult ↑? (→ no prescription for patients at risk!)
Cardiovascular protection? (if started right after menopause)	Cardiovascular risks (coronary heart disease/ atherosclerosis) ↑? (→ start only within the first 10 years after menopause and not in patients with cardiovascular disease!)

WHI study has been criticized by many experts and by the International Menopause Society [31] mainly due to some methodological limitations, e.g. mean age of 63 years and high prevalence of cardiovascular risk factors at study entry. The WHI re-analyses [32] have shown that the cardiovascular complications may be reduced by an early start of replacement therapy. Thus, there appears to be a window of opportunity for the potential cardiovascular benefits with HRT when replacement therapy is started early after the menopause [28].

Low and ultra-low doses of estrogens have been recently suggested for HRT [31] with transdermal application showing less side effects – with doses of 17β-estradiol varying from 14 to 25 µg. Whether low and ultra-low doses would have beneficial effects on mental well-being remains unclear.

Alternatives to Hormone Replacement Therapy

Compounds with more specific and potent estrogenic activity in the brain as opposed to other tissues are needed as an alternative to HRT. This would not only minimize side-effects of hormonal therapy, but may also allow new therapeutic strategies in men. Possible candidates are the selective estrogen receptor modulators (SERMs), whose agonist or antagonist properties depend on the target tissue. The effects of the existing SERMs (e.g. tibolone, raloxifen) on the brain, however, remain poorly studied.

Management of Premature Menopause

With growing evidence of altered gonadal function and premature menopause in schizophrenic females, the investigation of these patients should include questions regarding menstrual irregularities, amenorrhea, loss of libido, anorgasmia, infertility and galactorrhea; if estrogen deficiency is suspected, prolactin levels should be monitored. Hyperprolactinemia can theoretically be caused by the disease itself and the accompanying stress, but also by neuroleptic treatment, and can lead to secondary suppression of physiological estrogen production. Thus, many women treated with neuroleptics could suffer from a partially iatrogenic 'early menopause', with all the accompanied consequences, i.e. osteoporosis, enhanced cardiovascular risk and cognitive disturbances. In the case of neuroleptic-induced hyperprolactinemia with secondary estrogen deficiency, medication could be switched to a different agent with little or no associated hyperprolactinemia (e.g. quetiapine, aripiprazol, clozapine or olanzapine). As an alternative, estrogens could be added as an adjunct therapy to standard neuroleptic medication.

Management of Hormone-Drug Interactions

Estrogens may increase the efficacy of chlorpromazine [33], phenothiazines [34] and other antipsychotics [7]. With declining estrogen levels around the menopause, some women might benefit from dose adjustments of antipsychotics.

Other Medical and Psychosocial Aspects of Menopause in Patients with Psychoses

Medical Aspects

After the menopause, women are generally at an increased risk of developing a variety of medical disorders. Women with schizophrenia are even at an excess risk for many conditions, due to physical inactivity, poor diet, excessive smoking. Long-term neuroleptic treatment may also contribute to heightened morbidity, i.e. higher risk for metabolic syndrome, osteopenia or even osteoporosis.

Tardive dyskinesia seems to be more common and more severe in elderly women than men and seems to increase with age [35]. It has been suggested that estrogen withdrawal may contribute to this observation. Furthermore, thyroid function may be altered after menopause and influence mental well-being. Other frequent co-occurring medical illnesses in schizophrenia include diabetes, respiratory ailments and cardiovascular problems.

Unfortunately, schizophrenia patients are at great risk for greater medical neglect. Lindamer et al. [27] found that middle-aged and older women with schizophrenia were less likely to have had pelvic examination and PAP smears or mammograms

compared to women with no known diagnosis. Older schizophrenic women should therefore be carefully monitored regarding their physical health with routine physical check-ups including blood pressure, weight and laboratory tests (glucose, lipids, etc.), EEG, mammography and PAP smears.

Psychosocial Aspects

Women during menopausal transition are also often confronted with many psychosocial stressors such as changes in family roles and manifold losses. In many cases, women with diagnosis of schizophrenia usually have already a very small social network and quite often report loneliness and a lack of social support.

Treatment recommendations for women in this age group therefore should include psychosocial support, skills training, supported employment, social welfare, etc. Psychotherapy should not only pay special attention to the ongoing stressors and losses, but also to their subjective experience of the menopause including their physical symptoms, their fears and beliefs regarding the experienced changes, their femininity and sexuality.

Conclusions

The menopause transition endures an enhanced risk of first onset of schizophrenic psychoses. Postmenopause is associated with quite severe symptoms in psychotic women whereas the severity of symptoms tends to diminish in aging men. This observation should have many implications for the appropriate treatment strategy, which should consider not only the potential benefits of estrogen replacement but also the use of psychosocial interventions.

Promising studies suggest that the neuroprotective properties of estrogen could justify its use as an adjunctive strategy to traditional drug therapies in schizophrenia.

Consideration of the menopausal status should be part of standard clinical care for mentally ill women. The use of estrogens, however, should always be decided on the basis of an individual risk-benefit assessment [31] in close co-operation between psychiatrists and gynecologists.

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