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The forthcoming role of treatment with oestrogens in mental health

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Summary

Questions under study: An overview of the influence of the menopause on women's mental health is provided, with special emphasis on the role of oestrogens. Some controversial topics are highlighted, in particular the role of oestrogen-containing hormone replacement therapy as adjuvant treatment in mental disorders.

Methods: Selective review of literature.

Results: The gonadal source of oestrogen production is lost at the menopause. As oestrogens have important neuro- and psychoprotective activities, this loss may trigger or aggravate mental disorders in vulnerable women. Notwithstanding, the influence of menopause on mental health is still controverted, particularly since the publication of study results denying the potential benefits of oestrogen replacement therapy after the menopause. However, many of these studies suffer from methodological limitations and the ensuing discussion often fails to differentiate clearly between perimenopause and postmenopause, between menopausal transition and aging, between clear-cut mental disorders and minor changes in wellbeing. And, most importantly, authors often do not distinguish between prophylactic and therapeutic administration of oestrogens.

Conclusions: A subgroup of vulnerable women may suffer from the hormonal changes naturally occurring during the perimenopause and coinciding with the manifold psychosocial changes coming together during this phase of life. Oestrogen replacement therapy may be helpful in these cases but also carries some risks. More research is needed on the indications and contraindications for hormone replacement therapy in the context of mental disorders.

Key words: mental health; depression; psychosis; menopause; oestradiol; hormone replacement therapy

Introduction

The menopause usually occurs in women around the age of 52 years [1]. 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. Consequently, women now live more than one third of their lives during the postmenopause [2]. The mere length of this period justifies maximum concern for women's mental wellbeing and physical health during the menopausal transition and after the menopause (Tab. 1) [3].

In addition to the obvious physical aging occurring around the menopause, this phase of life is often burdened with numerous emotional stressors such as children leaving home, frequent sexual and relational problems, worries about the health of partner, parents or herself, stressful confrontation with biological aging itself and the need to reevaluate life expectations.

Table 1

Definitions of "Menopause", "Perimenopause" and "Postmenopause" (according to [3]).

Menopause:	The permanent cessation of menstruation, defined by the last menstruation, resulting from loss of ovarian activity.
Perimenopause:	The time period immediately before menopause – when hormonal, biological and clinical features of the menopause already commence – until the end of the first year after menopause.
Postmenopause:	The time period after menopause

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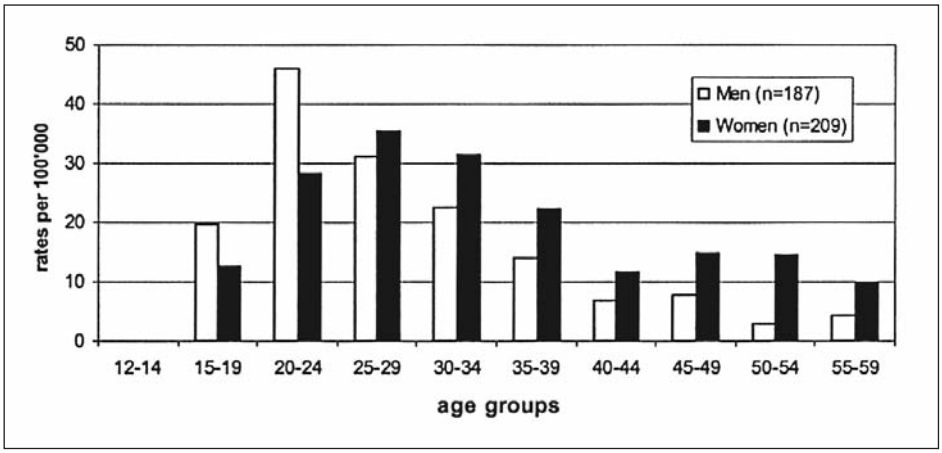

Figure 1

Sex-specific age-distribution of first admissions because of schizophrenia and paranoid psychoses (ICD-9 295, 297, 298.3 + .4) (according to Häfner et al. [6]).

Apart from these environmental changes, the sudden loss of oestrogen 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 oestrogens play a role in positively influencing mental wellbeing ([4, 5] for review). From the clinical viewpoint depressive symptoms and even an upsurge in the incidence of some severe mental disorders such as schizophrenia, have been observed around the menopause (Figure 1) [6], suggesting the direct involvement of instant loss of oestrogen activity in mental health.

However, in contrast to the well established effect of oestrogens on the *symptoms* of depression, the results of studies into the effect of oestrogens on depressive *disorders* as a disease, i.e. more severe depressive symptoms, are contradictory. This ongoing controversy may result from study-related methodological problems rather than lack of oestrogen effects. Thus, for example, single depressive symptoms are not always differentiated from depressive disorders. The latter are only diagnosable when specific diagnostic requirements regarding the constellation and severity of depressive symptoms, e.g. according to DSM IV or ICD-10 [7, 8], are met. Furthermore, many studies do not draw a clear distinction between the terms perimenopause and postmenopause (Table 1) [3], which is highly relevant since the perimenopausal transition appears to involve more depressive disorders when compared with the life span after the menopause. In addition, few studies distinguish between direct effects of an oestrogenic activity on the brain and indirect effects caused by an associated amelioration of vegetative symptoms [9–15].

In this communication we therefore discuss the implications of recent research findings on the use of oestrogen preparations for the treatment of mental disorders in peri- and postmenopausal women.

The influence of menopause and oestrogens on mental health

General neuroprotective and psychoprotective effects of oestrogens?

Oestrogens, 17-β-estradiol in particular, exert multiple positive functions in the brain, as they seem to improve both cerebral blood flow and glucose metabolism, promote neuronal sprouting and myelinisation, enhance synaptic density and plasticity, facilitate neuronal connectivity, act as antioxidants and inhibit neuronal cell death ([4, 16] for review). Basic research has long demonstrated these effects (Fig. 2) [17].

As long ago as the early eighties the identification of oestrogen receptors in the limbic system led to the assumption that oestrogens not only play a role in the modulation of endocrine functions but must also have a "neuro-modulating function" [4, 18]. It was observed in laboratory animals that the effect of oestrogens is in some respects similar to that of neuroleptics ([4] for review). Oestrogens modulate cerebral neurotransmission in many ways and influence both mood and cognition. They appear to have significant effects on the dopaminergic, serotonergic, noradrenergic, glutamergic and cholinergic systems. They influence gene expression but also have non-genomic rapid interactions, a fact which explains the different latency of effects [16, 18, 19].

Concurrently, ample evidence has been collected to show that oestrogens exert several positive effects on the mental state. They may act as mild antipsychotics [20–22], improve affective symptoms [18, 23], reduce aggressivity [24] and influence suicidal behaviour [25]. They may also act as stress protectors [26, 27] and effectively improve cognitive function [18, 28]. Oestrogens have therefore even been called "nature's psychoprotectants" [29].

However, some of these *positive* effects of oestrogens on brain functioning, e.g. regarding

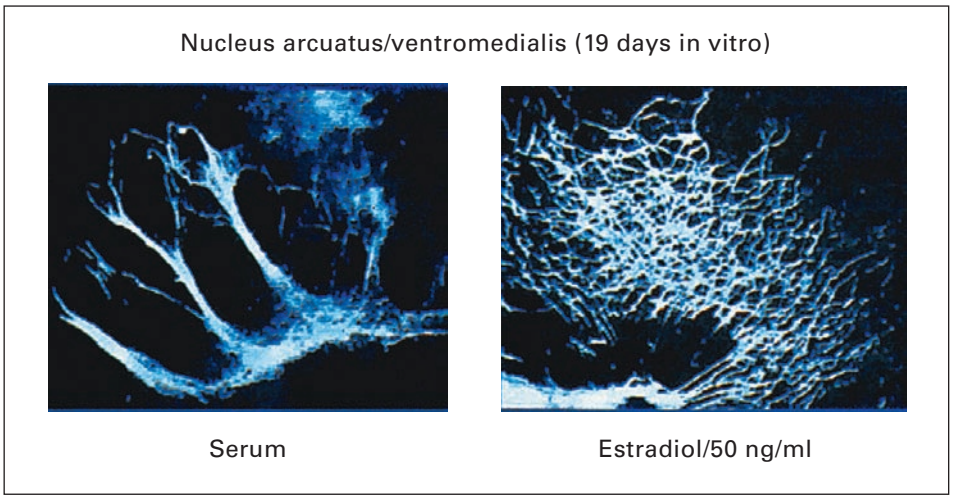

Figure 2

Neuritic proliferation in response to estradiol. (Explant of organotypic cultures from newborn mice).

cognitive function, have recently been questioned in the context of perimenopausal estrogen replacement [30]. Others have argued that oestrogens show their positive effects only in the presence of reduced endogenous oestrogen levels and that if oestrogen treatment is to be effective it must be started around the menopause [31].

This ongoing controversy has been exacerbated by the results of a large double-blind controlled study, the WHI study [32], which was set up to investigate the effect of long-term intake of hormonal replacement therapy (HRT) in elderly women. This study not only evidenced an unexpectedly high incidence of various complications (see below) during HRT but also a lack of effect on quality of life [33]. Another prospective study (HERS) was unable to detect a general improvement of depressive symptoms in women around the menopause [34]. Only in women suffering from severe hot flushes was some additional amelioration of depressive symptoms recorded.

However, in this context, the use of oestrogens for *therapeutic* reasons must be distinguished from their *prophylactic* use. Only the latter was investigated and criticised by the WHI study. At the moment HRT for *prophylactic* reasons remains valid only in young women in premature menopause or in osteopenic women with climacteric symptoms who are also at risk of osteoporosis.

With regard to mental disorders it also is essential to differentiate between *causal* factors on the one hand and *triggers* on the other. Taking schizophrenia as an example, abnormalities in the cerebral metabolism of dopamine and other neurotransmitters in genetically vulnerable women are thought to be involved in causing psychotic symptoms, whereas the loss of oestrogenic activity with its dopamine-modulating properties merely seems to trigger the outbreak of schizophrenia in some women around the menopause ([22] for review). Thus, the hormonal changes around menopause are probably very rarely the cause of mental disorders but may easily trigger the outbreak or relapse of a disorder, or worsen its course, in *vulnerable* women.

The effect of oestrogens in schizophrenia

Schizophrenia comprises a group of mental disorders of varying severity, which involve disturbances in thinking, perception, mood and behaviour. The course of schizophrenic psychoses is often a chronic recurrent one. The cause of these psychoses is still not really known, but involves a genetic predisposition in a sizeable proportion of all cases. Different genotypes have meanwhile been described with regard to a possible predisposition for schizophrenia: amongst others the met/val polymorphism of the *COMT* gene (located on chromosome 22), the *DISC1* gene on chromosome 1 and the neuroregulin1 (*NRG1*) gene [35, 36]. A further suspected risk factor for schizophrenia – at least in some individuals – is a history of brain damage during pregnancy or de-

Table 2

Neurotransmitter function in depression and schizophrenia – and oestrogen effects.

Neurotransmitter	Depression	Schizophrenia	Estrogen effects
Dopamin-D_2	↑↓	↑	↑↓
Serotonine	↓	?	↑
Noradrenalin	↓		↑
GABA	↓	?	↑
MAO	↑		↓

Modified according to Archer 1999 [37]

livery. Psychosocial stressors such as difficult infant-mother relationships, socioeconomic distress and others [35] then act as stressors which may provoke psychotic reactions in such vulnerable persons. These reactions themselves involve a massive disturbance in various neurotransmitters, e.g. dopaminergic hyperactivity during acute psychosis. The sudden fall in oestrogen levels during the menopause may contribute to the outbreak of schizophrenic psychotic reactions, since oestrogens may modulate many, and especially the dopaminergic, neurotransmitter functions ([22] for review). Psychotic disorders are usually treated with antipsychotic drugs, which help to normalise these neurotransmitters' activity. Oestrogens appear to reverse some neurotransmitter activities which are abnormal in both depression and schizophrenia ([37] for review) (Tab. 2). Two out of three genotypes associated with a preschizophrenic condition, neuroregulin 1 [38] and *COMT1* [39], are closely related to the downstream metabolism of oestrogens.

Various studies have demonstrated that oestrogens may have a protective effect in schizophrenia ([4, 22, 41] for reviews). In accordance with this theory Riecher-Rössler et al. [42, 43] demonstrated an excess of onsets and relapses of schizophrenia during the perimenstrual low oestrogenic phase of the menstrual cycle. They also showed that the level of psychotic symptoms correlates inversely with serum oestradiol levels during the menstrual cycle. Other clinical research groups have achieved similar results ([22] for review). It has also been demonstrated that schizophrenic women with intact menstrual cycles require less antipsychotic medication than postmenopausal women or men [40].

Further, various epidemiological studies have shown that schizophrenic psychoses begin on average 4–5 years later in women than in men (Figure 1) [6]. And, what is even more interesting, women also exhibit an additional smaller peak of onset of schizophrenia after age 45, denominated "late onset schizophrenia" [6, 44–46]. It has been postulated that this upsurge of late onset schizophrenia is caused by loss of the protective effect of oestrogens. According to this hypothesis, women are to some extent protected against schizophrenia during their reproductive life span by the relatively high gonadal oestrogen levels exhibited during this period. Then, around age 45, when oestrogen production begins to fall, vulnerable women without the protective action of oestrogens may become schizophrenic. In fact, the incidence of schizophrenia after the age of 40 was found to be twice as high in women as in men. While the onset of illness was after age 40 in only 10% of all schizophrenic men, this was true of 20% of all women [44]. Interestingly, the severity of the disease was more pronounced among these late onset women as compared with men at a similar age [44]. Furthermore, we know that *chronic* psychoses may deteriorate after the menopause ([44] for review).

First intervention studies in women with schizophrenia have been performed with conflicting, albeit promising, results. Kulkarni et al. [47, 48] showed that schizophrenic women receiving oestradiol as an adjunct to neuroleptic treatment show more rapid improvement of psychotic symptoms than women receiving neuroleptics only. In a recent Cochrane review on the use of oestrogens for schizophrenia, authors concluded that at the moment there are too few studies supporting the evidence for clinical use of oestrogens [49].

However, no studies at present focus on perior postmenopausal women. There is only a case report on a single postmenopausal woman with schizophrenia who benefited mentally from oestrogen replacement therapy [50]. Lindamer and co-workers [51] reported interesting results on a community sample of postmenopausal women with schizophrenia who received hormone replacement therapy from their gynaecologist for reasons other than psychosis. Interestingly, the users of HRT needed a relatively lower average dose of antipsychotic medication and suffered from less severe negative symptoms than the control group without HRT. Also in *postpartum* psychosis, oestrogen substitution induced a significant improvement [52].

The effect of oestrogens in depression

*Peri*menopause is clearly associated with an increase in depressive *symptoms*, but studies regarding depressive *disorders* are contradictory. However, more recent studies suggest that some women are particularly vulnerable to development of depression when entering the perimenopause, and that loss of oestrogens may trigger the onset of the disease in these women [53, 54]. Freeman et al. [55] in a large, methodologically very thorough recent study have shown that new onset of depressive disorder was 2½ times more likely to occur during the menopausal transition as compared with premenopausal women. And the Harvard Study of Mood and Cycles recently showed similar results [56]. Also *recurrence* of depression may occur more often during that period of life.

With regard to an increase of depressive disorders in *post*menopause, studies are even more contradictory and the more recent ones tend to be negative [13, 14, 57, 58]. The same is true of the so-called "gender gap", which refers to the fact

that depression is about twice as frequent in women as in men from young adulthood onwards. While some studies find a declining predominance of depressive disorders among women after menopause as compared with men, others suggest that the higher prevalence among women is maintained [59].

Interventional studies show clearer results, with quite positive therapeutic effects of oestrogens in depression. In women suffering from hot flushes, mild depressive symptoms may also be present and can be treated effectively with oestrogens without referral to a psychiatrist. The same therapeutic effect has also been demonstrated in surgical menopause [23]. Zweifel and O'Brien [60] have conducted a metaanalysis on 26 studies of mild depression. They concluded that oestrogen treatment has the potential to reduce mild depressive symptoms in women with a natural menopause. The therapeutic effect was most pronounced in perimenopausal women, as opposed to *post*menopausal or mixed study groups. Similar studies in *post*menopausal subpopulations have shown less compelling evidence of oestrogen's antidepressant efficacy ([61] for review).

Meanwhile, there have been studies also showing a favourable effect of oestrogen treatment in more *severe* depression meeting the DSM criteria. These studies concentrated on the perimenopause [62–65]. Only Cohen [62] also studied postmenopausal women, in whom there was no clear effect. Short term, low-dose oestrogen *augmentation* of antidepressant medication also appears to further improve mood in perimenopausal women with major depression who have had only partial remission of depression under antidepressants alone [66].

The potential future role of oestrogen treatment in mentally ill women

The preceding overview of the medical literature strongly suggests that substitution with oestrogens still has the potential to become a valuable treatment in women with mental disorders. Some of these could become a *therapeutic* indication for oestrogen replacement as opposed to oestrogens' *prophylactic* use, the latter being at present the target of sharp criticism.

Regarding ***depression***, oestrogens are obviously particularly helpful during the *peri*menopause. In these cases, a therapeutic trial seems justified, especially in mild depression or if there is an additional indication for oestrogen replacement such as hot flushes. For the *post*menopause more studies are needed.

As an alternative to treatment with oestrogen preparations selective serotonin reuptake inhibitors (SSRI) can also be used. These, however, carry their own risks. Benefits and risks of oestrogens versus SSRI must be carefully weighed. If oestrogens alone are not sufficient, or in more severe depression, antidepressants must be added. In these cases oestrogens may enhance endogenous serotonergic activity and thus induce a better responsiveness to SSRI [19, 67, 68]. Needless to state that medical treatment must always be coupled with psychotherapy and often also social support.

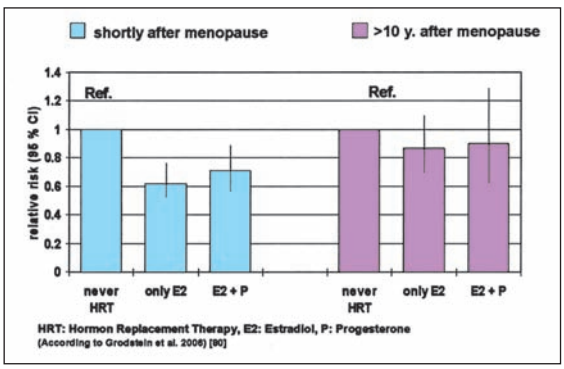

Figure 3

Nurses' Health Study: Risk of developing coronary heart disease according to menopausal status.

Theoretically, oestrogen replacement in the perimenopause could be helpful in women with ***schizophrenia*** as well. The relationship between some of the schizophrenia-susceptibility genotypes and the downstream signalling of oestrogen lends further support to this hypothesis. Apart from a positive effect on the mental state, oestrogens could attenuate perimenopausal complaints in these women, such as hot flushes and sleep disturbances, which in vulnerable women may act as stressors and provoke psychotic relapses. However, there is so far no published randomised, placebo-controlled, double-blind study of oestrogen replacement in peri- or postmenopausal women ([49] for review), and thus no clinical recommendation can yet be made.

Many women with schizophrenia also present with premature loss of ovarian function, mainly due to suppression of the gonadal axis by neuroleptics via hyperprolactinaemia. In these cases the medication should be changed to a prolactin-sparing neuroleptic such as quetiapine, aripiprazole, olanzapine or clozapine. If this is not possible for clinical reasons or does not normalise the hormonal status, oestrogen substitution may be necessary to avoid the long term consequences of sustained oestrogen deficiency.

Also, depression and antidepressants may be associated with premature menopause [69, 70]. This implies that standard clinical care for these severely ill women should always include questions regarding the gonadal axis as part of routine history-taking and close cooperation between psychiatrists, gynaecologists and general practitioners.

Risks of treatments with oestrogenic preparations

In recent years we have become much more aware of potential negative effects of oestrogens, such as thromboembolism or the risk of endometrial cancer [71]. To avoid the latter, oestrogens are administered in combination with gestagens in women with an intact uterus. Even in these women the above-mentioned Women's Health Initiative (WHI) study has demonstrated that the risks of stroke, coronary heart disease, pulmonary embolism and breast cancer are significantly increased in those cases [72, 73]. However, the WHI study has been criticised by many experts and by the International Menopause Society [74–76], mainly because the study population was much older than that around the natural menopause (mean age 63 years at inclusion). Many of the complications noted in the WHI study such as stroke, pulmonary embolism and myocardial infarction are caused by the vascular effects of oestrogens in the presence of manifest arteriosclerosis. On the one hand, at more advanced age the density of the alpha-oestrogen receptor in the vascular wall decreases, leading to a reduction of the protective effect of oestrogens. The density of the beta-oestrogen receptor in arteriosclerotic plaques increases with the extent of the inflammatory damage to the vascular wall [77]. In addition to these vascular changes, exogenous oestrogens may further activate the adherence of circulating thrombocytes to the arteriosclerotic plaques, thereby increasing the risk of thrombosis and embolism [78]. The biased conclusions due to the recruitment of many older patients have now been partially counteracted by reanalysis [79], in which at least the cardiovascular complications can be reduced by an early start to replacement therapy. This has opened a window of opportunity in which at least a cardiovascular benefit can be obtained in healthy menopausal women when replacement therapy is started early after the menopause (Figure 3) [80].

In addition, combined treatment with both oestrogens and gestagens is needed to prevent endometrial hyperplasia and endometrial cancer in women with an intact uterus. This combined treatment has been shown to carry a small incremental risk of breast cancer during long term use. If oestrogens can be used as monotherapy, particularly in women after hysterectomy, the risk of developing breast cancer appears to be smaller (although the difference was not statistically significant).

Conclusion

Even in recent studies such as the WHI study, psychiatric aspects have been much neglected. A substantial number of women may suffer from the menopause, some of them being vulnerable to mental illness. Certainly, the menopause is a *physiological* event, but it is accompanied by hormonal and other biological alterations as well as manifold psychosocial changes. All these changes can trigger or aggravate mental disorders in some women, probably on a basis of genetic susceptibility. Oestrogen replacement may in these cases be an effective *therapeutic* measure.

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