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

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
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<tbody>
<tr>
<td>Menopause</td>
<td>The permanent cessation of menstruation, defined by the last menstruation, resulting from loss of ovarian activity.</td>
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<tr>
<td>Perimenopause</td>
<td>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.</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>The time period after menopause</td>
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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 post-menopausal 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 myelination, 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...
cognitive function, have recently been questioned in the context of perimenopausal estrogen replacement [30]. Others have argued that estrogens 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**

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<tr>
<th>Neurotransmitter</th>
<th>Depression</th>
<th>Schizophrenia</th>
<th>Estrogen effects</th>
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<tbody>
<tr>
<td>Dopamin-D2</td>
<td>↑↓</td>
<td>↑</td>
<td>↑↓</td>
</tr>
<tr>
<td>Serotonin</td>
<td>↓</td>
<td>?</td>
<td>↑</td>
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<tr>
<td>Norepinephrine</td>
<td>↓</td>
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<td>GABA</td>
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<tr>
<td>MAO</td>
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Modified according to Archer 1999 [37]
The forthcoming role of treatment with oestrogens in mental health

Regarding depressive disorders, there is a notable 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 postmenopause, 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 menopause is clearly associated with an increase in depressive disorders, occurring more frequently during the menopausal transition as compared with premenopausal women. Also in postpartum psychosis, oestrogen substitution induced a significant improvement [52].

The effect of oestrogens in depression

Perimenopause 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.

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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 [39].

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 postmenopausal or mixed study groups. Similar studies in postmenopausal 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 perimenopause. 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 postmenopause 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.

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 perimenopausal 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 asquetiapine, 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.

Figure 3
Nurses’ Health Study: Risk of developing coronary heart disease according to menopausal status.
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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