Menopause and Mental Health

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Abstract

Menopause is a natural event, which women experience around age 50. It is defined as the final menstrual period and is preceded by many years of "menopausal transition" associated with marked biological and hormonal changes. Although it is a physiological process, especially the fluctuations and final loss of estrogen activity may have a negative impact on mental well-being; lead to vasomotor symptoms, sleep disturbances, sexual problems, cognitive decline, and depressive symptoms; and may even contribute to an upsurge in the incidence of severe mental disorders, such as depressive disorders or schizophrenic psychoses. In addition to these biological changes, for women this phase of life is often burdened with numerous psychosocial stressors, role changes, losses, and the experience of aging.

This has many implications for the clinic and for research. In the clinic the specific diagnostic and therapeutic needs of women of this age group have always to be taken into account. Appropriate treatment strategies should not only include specific psychotherapeutic and psychosocial interventions but also consider estrogen replacement where indicated in addition to standard psychiatric care. The latter of course has always to be based on a thorough individual risk-benefit assessment and decided on in close cooperation with gynecologists and the well-informed woman herself.

While many studies suggest a benefit in perimenopausal depression, there still is a lack of well-designed studies on the indications and contraindications of estrogen replacement in perimenopausal women at risk for or suffering from other mental disorders. Further research is needed, especially regarding perimenopause and schizophrenic psychoses, the relative risk of hormone replacement as compared to treatment with psychoactive drugs, or the best augmentation strategies. Last but not least, we need more research on psychotherapies addressing the specific needs of women of this age group.

Keywords

Menopause · Estrogens · Mood disorders · Schizophrenic psychoses · Hormone replacement · Psychotherapy

Introduction

Women typically experience menopause, defined as the final menstrual period, at a mean age of 49 years with a wide variation ranging from 46 to 52 years, as shown by Schoenaker et al. (2014) in a recent meta-analysis. Mean age might be lower in Africa, Latin America, Asia, and the Middle East (Schoenaker et al. 2014). The menopausal transition with menstrual cycle irregularities and hormonal changes already starts 5–8 years earlier (Roberts and Hickey 2016).

Menopause is a natural event, and transition to menopause is a physiological process which is associated with marked biological and hormonal changes. During

menopausal transition, the ovarian production of the hormones estrogen and progesterone decreases, accompanied by strong fluctuations of hormonal blood levels. Then, with menopause, hormone production of the ovaries and menstrual periods stop permanently, and women are no longer able to bear children. Especially the fluctuations and final loss of estrogen activity may have a negative impact on mental well-being; lead to vasomotor symptoms, sleep disturbances, sexual problems, cognitive decline, and depressive symptoms; and may even contribute to an upsurge in the incidence of severe mental disorders, such as depressive disorders or schizophrenic psychoses. In addition to these biological changes, for women this phase of life is often burdened with numerous psychosocial events and stressors of midlife and with the aging process (Hoga et al. 2015). Not only do they sometimes realize their physical aging quite harshly during this process, but at the same time often first health problems arise in themselves, their partners, or parents. Sexual and relational problems might occur. Children might leave the house. And women might feel the need to reevaluate their life expectations.

Nowadays, the average life expectancy of women in many societies exceeds 80 years. Consequently, women now spend more than one-third of their lives after menopause. This has not always been the case. Not more than one century ago, women's life expectancy was so low that they often did not live much longer than until the age of menopause. That means, historically we are confronted with a relatively new situation. The great challenge for doctors, psychiatrists, and psychotherapists now is to secure women's mental well-being and physical health during the menopausal transition and the long period thereafter.

What Is Menopause?

Definitions and Timespan

"Menopause" refers specifically to the last menstrual period, which can only be confirmed retrospectively. The term "perimenopause" (also called "menopausal transition" or "climacteric") refers to the period with irregular menstrual cycles prior to menopause through to a year after the last period. "Postmenopause" refers to all years following the final menstrual period (Table 1). According to the widely accepted STRAW (STages of Reproductive Aging Workshop) staging system, the perimenopause can further be subdivided into three stages: (i) early menopausal transition or early perimenopause with persistent irregularity of the menstrual cycle; (ii) late menopausal transition or late perimenopause, characterized by an interval of amenorrhea of $\geq$60 days in the prior 12 months; and (iii) early postmenopause, corresponding to the 1st year following the final menstrual period.

Apart from that, there can be "premature ovarian insufficiency/failure" with a cessation of menses prior to the age of 40 years, and there can be "surgical menopause," when ovaries are removed for various reasons.

Table 1 Definitions

Menopause	Permanent cessation of menstruation resulting from loss of ovarian follicular activity (at least 12 months amenorrhea)
Perimenopause	Period immediately before menopause – when endocrinological, biological, and clinical features of approaching menopause begin – till the end of the first year after menopause
Postmenopause	After menopause

Source: Riecher-Rössler and de Geyter (2007)

Physiological Changes

The main cause of the menopausal transition seems to be the natural depletion and aging of the finite ovarian reserve of oocytes. This is characterized not only by a marked decline and often dramatic fluctuations of sex hormones but also by increasing follicle-stimulating hormone (FSH) levels. Then, with menopause there occurs a sharp decrease in estradiol and progesterone production by the ovaries. This substantial fall in circulating estradiol levels impacts many tissues from the brain to the skin (see below).

General Symptoms

The main symptoms of menopause seem to be vasomotor symptoms, vaginal dryness/dyspareunia, difficulty sleeping/insomnia, and adverse mood/depression (Santoro et al. 2015). Table 2 shows an overview of all symptoms based on a review by Monteleone et al. (2018). Up to three quarters of all women experience vasomotor symptoms with hot flushes and sweating, sometimes followed by a feeling of cold and shivering (Monteleone et al. 2018). These symptoms, which continue for 4 years in approximately half of all women and in some women much longer, can massively influence the quality of life and sleep as well as work performance. About 30–60% of women suffer from vulvo-vaginal atrophy with vaginal dryness and pain during intercourse (Santoro et al. 2015; Monteleone et al. 2018).The prevalence of some symptoms seems to vary considerably between geographical regions and ethnicities (Monteleone et al. 2018).

Diagnosis

According to the National Institute for Health and Care Excellence (NICE) guidelines (Lumsden 2016), clinically menopause and perimenopause should be diagnosed as follows:

In otherwise, healthy women aged over 45 years with menopausal symptoms diagnose:

- Perimenopause based on vasomotor symptoms and irregular periods
- Menopause in women who have not had a menstrual period for at least 12 months (and are not using hormonal contraception)
- Menopause based on symptoms in women without a uterus

Table 2 Overview of menopausal symptoms

Central nervous system	Vasomotor symptoms
	Sleep disruption
	Depression and anxiety
	Cognitive changes
	Migraine
Skin, mucosal, and hair changes	Reduced skin thickness
	Reduced elasticity
	Reduced hydration
	Increased wrinkling
	Hair loss
Weight and metabolic changes	Weight gain
	Increased visceral adiposity
	Increased waist circumference
Sexual function	Decreased sexual desire
	Dyspareunia
Urogenital system	Vaginal dryness
	Vulvar itching and burning
	Dysuria
	Urinary frequency
	Urgency
	Recurrent lower urinary tract infections
Musculoskeletal system	Joint pain
	Sarcopenia

Source: Monteleone et al. (2018)

In younger women under age 45 years with menopausal symptoms and change in their menstrual cycle, an additional FSH test can be considered (with an increase of FSH indicating perimenopause).

Influence of Menopause on Mental Health

Controversial Issues

There are many controversial issues around the topic of menopause. Thus, for instance, there is a lot of discussion whether the incidence of mental disorders, such as depression, is really increased around or after menopause. And if so, the reasons for that are far from clear. Is it mainly the impact of hormonal changes occurring with menopause? Or is it more the influence of general biological changes emerging with aging? And/or is it rather the psychosocial changes happening during this age period in many women's lives? It has also been

questioned whether women in and around menopause really have specific diagnostic and therapeutic needs or whether this would be just a "medicalization" of a physiological process. Especially harsh and often led by ideology rather than by evidence were the discussions about hormone replacement for women in that age group.

In the following it will be tried to resolve these questions and controversies as far as possible.

Methodological and Other Problems

Research on the relationship between menopause and mental health shows some difficulties and methodological limitations, which shall be briefly described here before reviewing the results of studies.

First of all, "menopause" has sometimes not been clearly defined and not well distinguished from "perimenopause" and "postmenopause." Often, also no distinction was made between early and late postmenopause, although they differ in many respects. Furthermore, studies sometimes do not clearly state if results concern only natural or also premature or surgical menopause.

Many studies have only examined cross-sectionally. Certain questions, e.g., regarding an increase in the incidence of mental disorders, however, can only be answered by longitudinal studies. Longitudinal studies that did find associations between psychopathology and the menopausal transition used binary or dichotomized outcomes, which may be problematic from a methodological and conceptual point of view (Rössler et al. 2016). Some studies were conducted only retrospectively. Another problem is that some studies did not clearly differentiate between incidence and prevalence or between a simple deterioration of mental well-being and the onset of a severe mental disorder. Also, studies were often only based on clinical samples as opposed to community-based samples. Results of such studies cannot be generalized to the general population of all menopausal women.

Further problems arise from the fact that the interpretation of the impact of menopause on psychological symptoms is very difficult. Hence, it can be hard to differentiate between the influences of normal aging and those of menopausal transition, i.e., the manifold biological and psychosocial changes occurring during this time period anyway and the influence of hormonal changes.

Regarding the impact of the loss of sex hormones themselves, it is not clear if the main problem is the actual loss or rather the fluctuations of hormones and if it is only the direct estrogen effects on the brain or also the vegetative effects of fluctuating estrogens such as hot flushes and night sweats which influence mental well-being (domino theory). Finally, it has to be kept in mind that the menopausal transition usually should not be regarded as *causal* factor but rather as a trigger that can provoke mental symptoms or even disorders in predisposed, vulnerable women.

How Can Estrogens Influence Mental Health?

The main physiological changes during transition to menopause are the strong fluctuations and decrease of estrogen levels. These changes might negatively influence mental well-being, since at the same time estrogens are known to have many neuro- and psychoprotective properties.

This is especially true for 17-β-estradiol, the natural estrogen that is most active in the brain (McCarthy 2008). It is known to promote neuronal sprouting and myelination, to enhance synaptic density and plasticity, to facilitate neuronal connectivity, to act as an anti-inflammatory and antioxidant, to inhibit neuronal cell death, to improve cerebral blood flow and glucose metabolism, and it might mediate BDNF expression and activity and positively influence mitochondrial function (for reviews, see McEwen and Milner 2017; Riecher-Rössler 2017; Shimamoto and Rappeneau 2017). Most relevant in the context of mental health is the fact that 17-β-estradiol obviously can modulate different neurotransmitter systems, such as the serotonergic, the noradrenergic, the dopaminergic, the glutamatergic, and the cholinergic systems (for reviews, see Barth et al. 2015; Gogos et al. 2015; Riecher-Rössler 2017).

It has even been suggested that 17-β-estradiol should be regarded as a neurotransmitter itself (Balthazart and Ball 2006), and it has been called nature's psychoprotectant (Fink et al. 1996).

Estrogens not only act via the classical genomic pathway but also have non-genomic, rapid interactions. Estrogen receptors are expressed in many areas of the human brain associated with neuroendocrine function as well as with emotion, memory, and cognition. Estrogens seem to have multiple effects on mental functioning (for reviews, see Gillies and McArthur 2010; Watson et al. 2010; Riecher-Rössler 2017). They seem to increase affective symptoms (Soares et al. 2001; Rasgon et al. 2002; Schiff et al. 2005; Karsidag et al. 2012; Gleason et al. 2015; for reviews, see Gillies and McArthur 2010; Fischer et al. 2014; Soares 2014; Toffol et al. 2015), aggressive and suicidal behavior (for review, see Riecher-Rössler 2003), and cognitive functioning (for reviews, see Maki and Dumas 2009; Pompili et al. 2012b; Boss et al. 2014; Fischer et al. 2014; Weickert et al. 2015; Brzezinski et al. 2017); seem to be stress-protective (Goldstein et al. 2010; Albert et al. 2015); and have antipsychotic properties (for reviews, see Riecher-Rössler and Kulkarni 2011; Seeman 2012; Brzezinski et al. 2017).

Based on this short overview of estrogen's properties, it seems likely that the fluctuation and loss of this hormone in the perimenopausal transition might also influence women's mental health, at least in those who are vulnerable for developing mental problems.

Other Medical Aspects

Mental well-being of women in the perimenopause might deteriorate not only because of direct hormonal influences on the brain and the suffering from vegetative symptoms of menopause but also because of the manifold other physical problems

that can occur with declining estrogen levels (see Table 2). These problems overlap with the general physical process of aging. In women with mental disorders, there may be additional medical problems, as will be discussed in the sections below.

Psychosocial Influences

Women of the age group in which menopausal transition usually occurs, that is, age 40–55 years, are at the same time often also confronted with manifold losses, role changes, and psychosocial stressors (Hoga et al. 2015). Children might leave the home in this phase of women's lives. They might also lose their partners or parents and feel lonely. They might be burdened by the illness of parents, close relatives, or friends. They might have to face multiple role transitions privately and also professionally. For example, if they did not have a fulltime job during motherhood, they will have to newly define their professional goals. All in all, long established roles in partnership, family, and profession might have to be re-evaluated.

Complex Interactions

Some of these problems are interconnected with the menopausal changes. Thus, for example, night sweats might contribute to sleep disturbances, resulting in irritability and as a consequence of this possibly also relationship problems. The loss of libido or dyspareunia some women experience might contribute to partnership problems or at least not be helpful in resolving them. The relationship problems then might contribute to depressive symptoms. Skin and hair changes as well as weight gain induced by hormonal changes might reduce self-esteem and thereby further contribute to the development of depression. Changes in the muscular-skeletal system with joint pain might prevent women from physical activities and sports, which usually would be protective factors for mental health and helpful coping mechanisms.

All in all, there seems to be quite a lot of interplay between aging, hormonal changes, and psychosocial changes in women of this age group, which can make them especially vulnerable.

Menopause and Specific Mental Disorders

Mood Disorders

Depression

Perimenopause seems to be clearly associated with an increase in depressive *symptoms*. However, there has been an ongoing debate whether it is also associated with an increased incidence of major depressive *disorders* (Riecher-Rössler and de Geyter 2007; Soares 2014; Rössler et al. 2016). First prospective cohort studies had not found an association between menopausal transition and mood (Vesco et al. 2007),

while more recent longitudinal studies performed in the USA have reported an increase of depressive symptoms (Cohen et al. 2006; Freeman et al. 2006; Bromberger et al. 2010, 2011) and major depression (Cohen et al. 2006; Freeman et al. 2006; Bromberger et al. 2010, 2011).

Thus, Freeman et al. (2006), in a population-based cohort of 231 women aged 35–47 without previous depression, whom they followed up for 8 years, found new onset depressive disorders to be 2.5 times more frequent during the menopausal transition as compared to premenopause. Depressive symptoms correlated with an increase of FSH, LH, and inhibin B and a greater variability of estradiol and FSH, suggesting that fluctuating rather than absolute hormone levels trigger depressive symptoms. They concluded that cyclic fluctuations of estradiol might have a destabilizing effect on women's mental health. Similarly, Cohen et al. (2006), in a population-based cohort of 643 women aged 36–45 without previous depression (follow-up 36 months), found a twofold increase of depressive symptoms and depressive disorders during menopausal transition, especially in those with hot flushes. Depressive symptoms were additionally associated with adverse life events. Interestingly, depressive disorders were not increased in women who took hormone replacement. Bromberger et al. (2010, 2011), in two population-based cohorts of 3,302 and 221 women aged 42–52 during a follow-up of up to 10 years, found a significant increase of depressive symptoms and a two- to fourfold increase of major depressive disorders in the perimenopause and early postmenopause. This finding was independent of the presence of vasomotor symptoms or stressful life events. A history of depression was the strongest predictor of depression.

In the Zurich study (Rössler et al. 2016), 168 women from a population-based Swiss community cohort study were prospectively followed up from age 21 to 50. Irritability/nervousness was increased in perimenopausal women, but not the prevalence rates of major depressive episodes. Preceding mental health problems and neuroticism trait scores as well as concurrent psychosocial distress were significantly related to mental health problems occurring between ages 41 and 50.

With regard to risk factors for depressive symptoms in the menopausal transition, some studies pointed to psychosocial factors such as changes in family structure and losses, role transitions, stressful or adverse life events, or low social support (Weissman 2000; Hardy and Kuh 2002; Cohen et al. 2006; Vesco et al. 2007; Bromberger et al. 2010). Personality traits like neuroticism might be another predictor (Li et al. 2008; Rössler et al. 2016). However, most studies found prior depression to be the main risk factor, particularly prior depression that was related to hormonal changes, e.g., prior postpartum depression or prior premenstrual mood dysphoric disorder (PMDD) (Freeman et al. 2004; Vivian-Taylor and Hickey 2014). This suggests that belonging to a subgroup sensitive to estrogen withdrawal increases the risk for developing depressive symptoms in the menopausal transition (Bloch et al. 2000). Furthermore, a decline in physical health, in libido, and in the "reproductive potential" as well as negative attitudes to aging and menopause may negatively impact on mood (Vivian-Taylor and Hickey 2014). Women who suffer from general menopausal symptoms such as hot flushes, sleep disturbances, or vasomotor symptoms also seem to be at increased risk for depressive symptoms

Table 3 Risk factors for depressive symptoms in the menopausal transition

Prior depression
Belonging to a subgroup sensitive to estrogen withdrawal (e.g., prior postpartum depression, or premenstrual mood dysphoric disorder)
No hormone substitution
Surgical menopause
Late or prolonged menopausal transition
Hot flushes, sleep disturbances, vasomotor symptoms
Psychosocial factors:
Changes in family structure, losses, role transitions
Stressful or negative life events
Low social support

Sources: Bloch et al. (2000), Weissman (2000), Dennerstein et al. (2004), Freeman et al. (2004), Freeman (2010), Bromberger et al. (2010), Kornstein et al. (2010)

(Freeman et al. 2004; Freeman 2010; Bromberger et al. 2010). The same might be true if the menopausal transition is very late or prolonged (Dennerstein et al. 2004; Kornstein et al. 2010), if there is an abrupt surgical menopause (Dennerstein et al. 2004) and no hormonal substitution (Dennerstein et al. 2004). So, all in all, prior depression seems to be the main risk factor for perimenopausal depression. Estrogen withdrawal and fluctuations seem to play a role as trigger especially in a subgroup sensitive to this. Psychosocial stressors can be additional triggers interacting with biological changes (Table 3).

With regard to later *post*menopause, studies are more contradictory (for review, see Riecher-Rössler and de Geyter 2007). In this context, it is very interesting to look at the so-called gender gap in the incidence and prevalence of depression, which refers to the fact that depressive disorders are about twice as frequent in women as in men from young adulthood onwards (Seedat et al. 2009; Steel et al. 2014; Boyd et al. 2015; Jacobi et al. 2015), and this preponderance of women in depression continues into old age as a recent epidemiological modelling based on 98 million cases globally showed (Ferrari et al. 2013).

It has also been shown that depression in younger women is sometimes associated with early ovarian insufficiency long before the normal age of perimenopause. The reason for this and the causal direction are not clear. It might be due to the stress associated with depression and/or antidepressant medication (Young et al. 2000; Harlow et al. 2003).

Schizophrenic Psychoses

Also the risk for women of developing schizophrenic psychoses around the age of menopause is significantly increased.

Already in the last century, Manfred Bleuler noted that "late-onset schizophrenia," i.e., schizophrenia with onset after age 40, was much more frequent

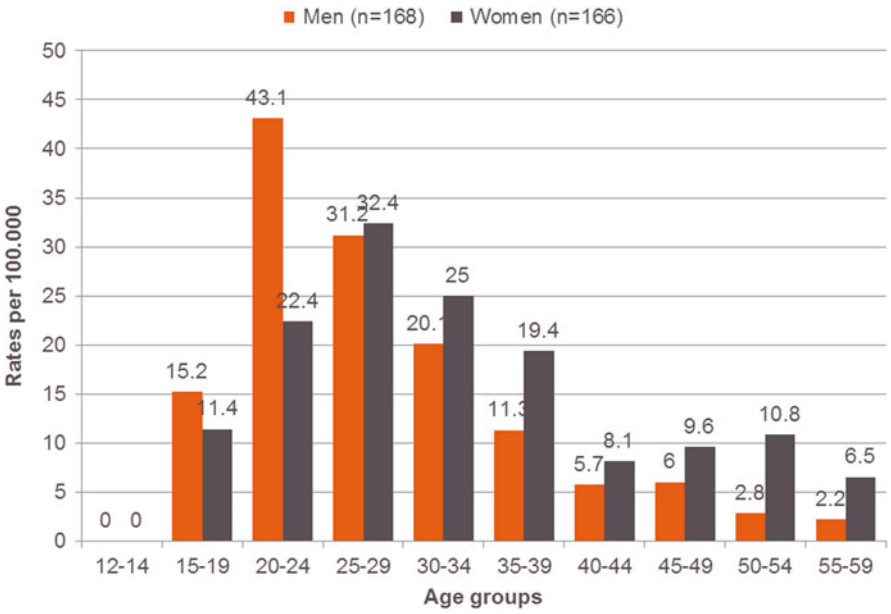

Fig. 1 Sex-specific age distribution at first admission for schizophrenia, narrow definition (ICD-9: 295) (ABC study). For broad definition (ICD-9: 295, 297, 298.3; 298.4) (see Häfner et al. 1991a, b)

in women than in men, a finding he attributed already then to the "loss of ovarian function" starting at around that age (Riecher-Rössler and Häfner 1993). In a study of a large representative population of 392 first-admitted patients with schizophrenic psychoses from a big catchment area of 1.5 million inhabitants (Riecher-Rössler et al. 1997), we were able to replicate this finding on a methodologically sound basis. The incidence of schizophrenic psychoses in the age group 40–60 years was about twice as high in women as in men. First admission for schizophrenic psychoses after age 40 occurred in only 10% of all men but in about 21% of all women. The first signs of the disorder had occurred on average 4 years before first admission in both sexes. The yearly incidence rate in women over age 40 was 8.9 per 100,000 inhabitants, whereas it was only 4.2 per 100,000 inhabitants in men (Riecher-Rössler et al. 1997) (Fig. 1). Various epidemiological studies have in the meantime confirmed that women develop schizophrenic psychosis on average 4–5 years later than men and also exhibit an additional peak of onsets after age 40 (Riecher-Rössler 2017).

These findings have been explained with the "estrogen protection hypothesis," which postulates that estrogens, especially 17-β-estradiol, are protective against psychosis (Riecher-Rössler and Häfner 1993). This hypothesis has ever since gained support from many laboratory, epidemiological, and clinical studies (for review, see Riecher-Rössler 2017).

According to the estrogen hypothesis, women are to some extent protected against schizophrenia between puberty and menopause by their relatively high gonadal estrogen production during this time (Riecher-Rössler and Häfner 1993). They therefore develop the disorder on average 4–5 years later than men (Häfner et al. 1991a, b, c). Then, after age 40, several years before menopause sets in, estrogen production begins to fall, and thus women lose the protection of estrogens, which could account for their second peak of illness onset after age 40 years (Riecher-Rössler and Häfner 1993).

In addition, we had a very interesting finding regarding the symptomatology and disease course of these late-onset women: Men with onset over age 40 showed significantly milder symptoms and spent less time in hospital than early-onset men, whereas late-onset women suffered from the disease almost as severely as patients who fell ill early in life (Riecher-Rössler et al. 1997).

An explanation for this could again be the protective effect of estrogens: If illness onset in women with a relatively high vulnerability is delayed by estrogens, this high vulnerability will be "unmasked" by the loss of estrogen protection around the time of the menopause (Riecher-Rössler et al. 1997). This would explain why these women 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, this may be related to the depletion of dopamine receptors with age – a decline which seems to be more precipitous in men than in women (Riecher-Rössler 2009).

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 (for review, see Riecher-Rössler 2003, 2005).

In this context, it is important to note that the loss of estrogens certainly is not a causal factor for psychosis but rather a trigger or biological "stressor" in the vulnerability-stress model of the pathogenesis of psychoses. 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 estrogenic activity with its dopamine-modulating properties merely seems to trigger the onset in vulnerable women around menopause or might worsen its symptomatology and course.

Premature Ovarian Insufficiency in Women with Schizophrenic Psychoses

Many women with schizophrenic psychoses also seem to suffer from premature ovarian insufficiency or failure. They show menstrual irregularities and reduced blood concentrations of estradiol and progesterone as well as abnormalities of gonadotrophins (follicle-stimulating hormone, luteinizing hormone) accompanied by anovulation and reduced fertility (for review, see Riecher-Rössler 2017). This premature ovarian failure is probably mainly due to hyperprolactinemia, which can suppress gonadal function and is often found in patients with schizophrenic psychoses (Riecher-Rössler 2017). Hyperprolactinemia is a side effect of many antipsychotics but obviously also occurs independently from antipsychotics. Thus, the above-named clinical signs have also been shown long before the introduction of

antipsychotics. And women with first episode psychosis retrospectively often reported signs of ovarian insufficiency long before the onset of the disease (Riecher-Rössler 2002). Recently hyperprolactinemia has also been shown in antipsychotic-naïve first episode psychosis or even in at-risk mental state patients, particularly in women.

As a consequence, women with psychosis might develop reduced bone mineral density (Markham 2012; Maric et al. 2005) and possibly other problems connected to the early loss of estrogens – similar to those of natural menopause (Riecher-Rössler et al. 1998, 2009) (see above).

Therapy and Prophylaxis

Estrogenic Replacement

Intervention Studies

In women with mental problems during menopause, many intervention studies with estrogen replacement have been performed, especially in depression (Soares et al. 2001; Rasgon et al. 2002; Schiff et al. 2005; Karsidag et al. 2012; for reviews, see Riecher-Rössler and de Geyter 2007; Gordon and Girdler 2014; Fischer et al. 2014; Soares 2014; Rubinow et al. 2015; Toffol et al. 2015) but also in schizophrenic psychoses (for reviews, see Brzezinski et al. 2017; Riecher-Rössler 2017).

In women with *schizophrenic psychoses*, the addition of transdermally delivered 17-β-estradiol to standard antipsychotics seems to be associated with a significant reduction of psychotic and other, particularly depressive, symptoms and potentially also with cognitive improvements (for review, see Riecher-Rössler and Kulkarni 2011). However, most studies have been performed in young women, although the greatest effect of estrogen treatment would be expected in *peri- and postmenopausal* women with estrogen fluctuations and deficiency. There was only a small study by Good et al. (1999) in postmenopausal women with schizophrenic psychoses who showed a significant improvement of verbal memory with hormone replacement. A community study of postmenopausal women with schizophrenia showed less severe negative symptoms in those with hormone replacement therapy. Furthermore, in this study hormone replacement therapy seemed to reduce the need for antipsychotics, as shown by lower doses (Lindamer et al. 2001). There are also some case reports with positive results of hormone replacement therapy in postmenopausal women with schizophrenia (Lindamer et al. 1997; Bergemann et al. 2007).

In women with *perimenopausal depression*, intervention studies with estrogens show clearer results with quite positive therapeutic effects. In a first meta-analysis of 26 studies, estrogen substitution was shown to be helpful in mild depressive symptoms, especially in the perimenopause, less so in postmenopause (Zweifel and O'Brien 1997). Also more recent randomized placebo-controlled studies showed significant positive effects of estrogen replacement on mood (Onalan et al. 2005; Schiff et al. 2005; Karsidag et al. 2012). They have found estrogens even to be effective in depressive disorders fulfilling DSM criteria (Schmidt et al. 2000; Soares

et al. 2001; Rasgon et al. 2002; Cohen et al. 2003; Morgan et al. 2005). There are also studies at odds with this finding (Morrison et al. 2004; Kornstein et al. 2013). Thus, in the (STAR∗D) study women with hormone replacement had no better remission than those without (Kornstein et al. 2013). On the other hand, it has to be noted that many studies were small, started with hormone replacement only years after menopause or used less potent forms of estrogens (Wharton et al. 2013). Or they did not treat women with depression but rather measured the effect on mood in healthy women (Onalan et al. 2005; Gleason et al. 2015).

Recent studies suggest that especially transdermally applied 17-β-estradiol shows very good remission rates in women with onset of depression during perimenopause (for review, see Gordon and Girdler 2014). This is probably due to the fact that 17-β-estradiol is the estrogen most active in the brain and also shows the best bioavailability and the most constant blood concentrations. The latter is believed to be important to stabilize the fluctuating estrogen levels and thereby to reduce women's sensitivity to stress (Gordon and Girdler 2014).

Critical Reappraisal of Estrogen Replacement

Estrogen replacement in perimenopause and postmenopause has been challenged by several studies, especially by the Women's Health Initiative (WHI) study, because of suspected side effects (Hlatky et al. 2002; Rossouw et al. 2002). However, the WHI study was criticized by many experts (Birkhäuser et al. 2008; Santen et al. 2010; Gurney et al. 2014) for methodological flaws, particularly the high age of the women studied (mean age 63) and their high prevalence of cardiovascular risk factors. Thus, many of the complications reported were probably associated with pre-existing risk factors. A reanalysis of the WHI data could not confirm the complications, but rather showed a cardiovascular benefit when estrogen replacement was started early after menopause (Rossouw et al. 2007). There seems to be a "window of opportunity" for starting hormone replacement (Rossouw et al. 2007; Santen et al. 2010; Azcoitia et al. 2011; McCarrey and Resnick 2015). Furthermore, the WHI study had used continuous conjugated equine estrogen rather than physiological estradiol which is known to have fewer side effects. They also gave it orally rather than transdermally as recommended in the meantime. And they combined it with the progestogen medroxyprogesterone acetate, which may be responsible for a slightly increased risk of breast cancer if given for more than 7 years (Santen et al. 2010; Cobin et al. 2017). If treatment starts early and 17-β-estradiol is given, also a protective effect on memory has been shown (Sherwin 2005; Azcoitia et al. 2011). A recent meta-analysis has indicated an increased risk for certain ovarian cancers (Collaborative Group on Epidemiological Studies of Ovarian Cancer et al. 2015), a finding which certainly has to be further studied. However, a recent meta-analysis on 43 RCTs found menopausal hormone therapy not to increase mortality, neither all-cause nor cardiac deaths or those from stroke or cancer (Benkhadra et al. 2015) (see also Table 4).

A very important argument in the controversy about the advantages and disadvantages of estrogen substitution is the distinction between a preventative application and a therapeutic use. In women with a mental disorder, estradiol would be used

Table 4 Some important effects of estrogen replacement in the menopause

Positive	
Perimenopausal complaints ↓	
Physical: hot flushes, genital discomfort, aging of collagen (skin, joints, intervertebral discs) ↓	
Mental: depression, irritability, emotional lability, sleep problems in those with vasomotor symptoms (psychotic symptoms?) ↓	
Risk of osteoporosis and fragility fracture ↓	
Delay of cognitive decline and Morbus Alzheimer?	
Cardiovascular protection? (only if started right after menopause)	
Negative	
Endometrial carcinoma ↑ if unopposed estrogens are administered	→ In women without hysterectomy combine with micronized progesterone!
Risk of breast cancer ↑? probably due to combination with progestogen	→ Do not apply in patients with a familiar or own risk and usually not longer than 7 years!
Risk of thrombosis and cerebral insult ↑?	→ No prescription for patients at risk!
Risks of coronary heart disease ↑?	→ Rather use 17-β-estradiol and transdermal application
	→ Start only within the first 10 years after menopause and do not apply in patients aged >60!
Risk of ovarian cancer ↑?	

Sources: Rossouw et al. (2007), Riecher-Rössler (2009), Santen et al. (2010), Pompili et al. (2012a), NICE guideline – Menopause: diagnosis and management (2015), de Villiers et al. (2013), L'Hermite (2013), Rozenberg et al. (2013), Gurney et al. (2014), Cobin et al. (2017), Collaborative Group on Epidemiological Studies of Ovarian Cancer et al. (2015), Cintron et al. (2017), The 2017 hormone therapy position statement of The North American Menopause Society (2017)

therapeutically. Potential side-effects here would have to be outweighed by the benefits and compared to the side effects of antipsychotics and other adjunct medications. *Prophylactic* estradiol replacement as used in the WHI study has to fulfil much higher safety requirements. Nevertheless, it was suggested by a recent study for prophylaxis of depression in perimenopausal and early postmenopausal women (Gordon et al. 2018).

In any case, pros and cons have to be carefully assessed in each woman individually, and the final decision has to be made by a well-informed woman herself based on an individual risk-benefit assessment. It goes without saying that estrogens should only be substituted in women without risk factors, in close cooperation with a gynecologist, and with close monitoring. The challenge here is that after the first alarming results of the WHI study (Rossouw et al. 2002), not all professionals and patients have been kept updated with newer, contrasting results and now "overestimate the risks and contraindications, and underestimate the impact of menopausal symptoms on a woman's quality of life" (NICE guideline – Menopause: diagnosis and management 2015).

Psychiatrists should have sufficient knowledge to be advisors of their patients and cooperation partners of gynecologists. To this end they should know the best mode of hormone replacement (Riecher-Rössler and Kulkarni 2011). The natural

Table 5 Therapy of depression in perimenopausal women – indications for estrogen replacement

In perimenopause (not in postmenopause)?
Especially, if first lifetime onset in perimenopause
If estrogen-sensitive depression (history of PMDD or of postpartum depression)
In mild to moderate depression
If no risk factors/contraindications
If a well-informed woman wishes estrogens
If additional indications for estrogen replacement (e.g., no FDA approval for depression)
For therapy, not prophylaxis
Not after age 60
Use of 17-β-estradiol
Low dose
Prefer transdermal application
For endometrial protection a progestogen has to be added (unless patient had hysterectomy). Prefer low-androgenic progestogens and add sequentially (e.g., micronized nature-identical progesterone, dydrogesterone, or cyproterone acetate)

Bloch et al. (2000), Schmidt et al. (2000), Altshuler et al. (2001), Joffe et al. (2003), Riecher-Rössler and de Geyter (2007), Birkhäuser et al. (2008), McCarthy (2008), Sturdee et al. (2011), Rozenberg et al. (2013), Gordon and Girdler (2014)

17-β-estradiol seems to be the estrogen with the best benefit-risk profile and transdermal application (patches or gel) to have fewer side effects (L'Hermite 2013). Progestogens have to be added to estrogens for endometrial protection if a woman still has her uterus. Here the natural, "body identical," micronized progesterone seems to be the one with the least side effects (L'Hermite 2013).

Consequences for Prophylaxis and Therapy

Taken together, hormone replacement in the perimenopause is a possible therapeutic option for some women after careful consideration of pros and cons. In women with *schizophrenic psychoses*, it could be used as an augmentation strategy/adjunct to antipsychotic medication. Possibly the dose of antipsychotics could then be reduced and corresponding side effects of antipsychotics minimized.

Also in women with perimenopausal depression, hormone replacement could be an option, especially in certain cases as summarized in Table 5. In some cases of only mild depression, this treatment might be sufficient. In women with more severe depression, antidepressants are also needed (Riecher-Rössler and de Geyter 2007; Birkhäuser et al. 2008; Sturdee et al. 2011).

It has to be noted that there is no official approval in many countries for estrogen replacement for treating mental disorders, but there are often additional approved indications for its use in the individual woman. Thus, estrogen replacement for women of this age group has been recommended, for example, as prophylaxis of osteoporosis. Most importantly, estrogen replacement in women with mental disorders might not only have direct but also indirect positive effects on mental well-being. Thus, by attenuating perimenopausal complaints such as hot flushes, night sweats with sleep disturbances, and general irritability, it might contribute to a

general improvement of the mental state and prevent relapses. Other important positive effects of estrogens for these women could be the supposed improvement of cognition, stress vulnerability, aggression, and suicidality (see above and Table 4).

Further research into estrogen treatment as additional indication in perimenopausal women with schizophrenic and depressive disorders is urgently needed.

Novel Compounds: SERMs and Other Hormones

Alternatives to conventional hormone replacement are being investigated to avoid the side effects of hormonal therapy. Possible candidates are selective estrogen receptor modulators (SERMs) which – depending on the target tissue – have agonistic or antagonistic properties. Raloxifene, for example, which exerts its main effects on the bone, might also act on different brain receptors (Landry et al. 2002). In postmenopausal women with schizophrenia, it might improve negative and total symptoms and possibly also cognition (for reviews, see Seeman and Fitzgerald 2000; Riecher-Rössler 2017). In a recent meta-analysis, Wang et al. (2018) also found beneficial effects on psychotic symptoms in postmenopausal women with schizophrenia. It might also improve depressive symptoms (Usall et al. 2011). However, results are variable, which might be due to different individual genetic profiles of women (Gonzalez-Rodriguez and Seeman 2018). Although the use of raloxifene is relatively safe, a low risk of blood clots and deep vein thrombosis was reported (Cobin et al. 2017; Weickert et al. 2015) as well as other risks and side effects (Gonzalez-Rodriguez and Seeman 2018).

Management of Premature Menopause

As there is growing evidence for quite a number of women with depression and especially with schizophrenic psychoses having a premature ovarian insufficiency, this condition should be taken more seriously in future. That means that history taking also in younger women should always include questions regarding menstrual irregularities, amenorrhea, loss of libido, anorgasmia, infertility, and galactorrhea. If there are any clinical suggestions of estrogen deficiency, prolactin levels should be tested. In case of hyperprolactinemia, prolactin-sparing antipsychotics should be preferred (Riecher-Rössler 2017). However, switching to such an antipsychotic cannot be done without prior contraception counselling, because when prolactin production has gone back to normal, gonadal function and ovulation will be restored with a high risk of unplanned pregnancy. Alternatively, if switching the antipsychotic is not an option, hormone substitution even in these young women has to be taken into consideration (Riecher-Rössler 2017).

Psychopharmacotherapy

Psychopharmacotherapy for peri- and postmenopausal women should follow the usual guidelines for the respective disorder. Estradiol can be used in a first step or added as an adjunct in the above described cases.

Generally, there seems to be a lack of attention to the special needs of peri- and postmenopausal women regarding psychopharmacotherapy. Special requirements for women should always be considered, such as gender differences in pharmacodynamics and pharmacokinetics or the interaction of medication with sex hormones (for review, see Haack et al. 2009; Sramek and Cutler 2011; Gonzalez-Rodriguez and Seeman 2018).

Selective serotonin reuptake inhibitors (SSRIs) are not only effective against depression but also seem to reduce hot flushes and can be used for this indication in women who cannot or do not want to use estrogens (Cobin et al. 2017). In this context it is important to note that estrogens increase serotonergic activity in the brain and that postmenopausal women show a decreased response to SSRI (Sramek and Cutler 2011), while perimenopausal women *with hormone replacement* show an improved response to SSRIs (Stahl 2001; Morgan et al. 2005). As a caveat it has to be noted that in breast cancer patients, fluoxetine and paroxetine can often not be used because they inhibit the effect of tamoxifen (Cobin et al. 2017).

In women with schizophrenic psychoses, an increase of metabolic, cardiovascular, and neurologic side effects, such as tardive dyskinesia, was described (Gonzalez-Rodriguez and Seeman 2018; Seeman and Fitzgerald 2000). Therefore, antipsychotic treatment may need to be modified, and cardiac and metabolic health indices need to be more closely monitored (Seeman 2013). This increase of side effects in postmenopausal women might be due to estrogen withdrawal (Seeman and Fitzgerald 2000) and might also be a consequence of the higher doses of antipsychotics required after menopause due to increasing psychotic symptoms (Gonzalez-Rodriguez and Seeman 2018).

Psychotherapy

Psychotherapy in this age group should not only pay special attention to the manifold ongoing stressors and losses but also to women's subjective experience of the menopause, including their physical complaints, their fears and beliefs regarding menopause and the experienced changes, and their femininity and sexuality (Hoga et al. 2015).

Psychotherapy for women in general has to consider sex-specific risk and influencing factors. This is not only true for younger women but also for women in the perimenopause. Gender-specific socialization, gender roles, and gender role stereotypes as well as low self-esteem have often prevented women from pursuing their goals. With all the role changes in the age around perimenopause, they might for the first time realize this. Old, suppressed role conflicts might get virulent and have to be worked on in psychotherapy.

The role changes often imposed on women in this age group should be addressed as should the ongoing burdens and conflicts, such as dependencies in partnership and professional life – be it emotionally or financially – or experiences of discrimination, violence, and abuse (Garcia-Moreno and Riecher-Rössler 2013). Further topics can be the lack of appreciation women often experience, especially in this age group, or

the lack of support or poverty. All these are risk factors for depression (Kuehner 2003, 2017). Women in this age group are also often burdened by the problems of others in their social network, which has been called "cost of caring." Psychotherapy should help women to cope with the multifold role changes, conflicts, and burdens and to develop more self-confidence. Women often have to be "empowered" so that they can actively cope with their situation, discover their resources, pursue their goals, or redefine them. Most importantly, psychotherapy should enable women to counteract their well-known tendency to internalize conflicts, to ruminate, and to develop feelings of insufficiency and guilt and thereby depression (Nolen-Hoeksema 2012; Riecher-Rössler 2016; Belz and Riecher-Rössler 2017).

Women with schizophrenia, moreover, often have a very small social network and suffer from loneliness, which might even get worse with aging. They often have not married, are not in stable partnerships, and have no children. Previously supportive parents might now not be able to care for their daughter anymore, or the death of the parents might mean that she loses her main relationships. They might also lose other relatives or caretakers. They might not have regular work and contact with colleagues, and their socioeconomic situation might be especially poor, which might be even more stressful with increasing age. Thus, women with schizophrenia often need a lot of social support, especially in this age group around and after menopause.

Other Therapeutic Approaches

Treatment recommendations for women in this age group of course do have to consider not only hormone replacement, medication, and psychotherapy but also women's physical condition and their social needs and desires. Ultimately, a combination of effective biological plus psychosocial treatments tailored to the patient's individual needs, to her illness, as well as to the age group and the menopausal status are needed.

Complementary and "alternative" medicine has become increasingly popular in the last decades (Peng et al. 2014), especially after the confusion about risks and benefits of hormone therapy. In the meantime, a wide array of botanic medicine is offered, but evidence on efficacy and safety is very limited (Taylor 2015; Comhaire and Depypere 2015; Peng et al. 2014).

More methodologically rigorous studies in this area are needed and a better communication between health-care providers and patients. Women also require more information about menopause and the physiological changes occurring with it, in order to increase self-management and improve symptom management and coping strategies (Yazdkhasti et al. 2015). Menopause awareness has to be increased and the stigma often still associated with it to be challenged. Courses for such empowerment have been developed (Bellot et al. 2018).

As described above, in addition to their mental problems women might suffer from manifold physical problems due to menopause, both often being very much intertwined. Women with mental disorders are even at an excess risk for physical problems. This can be on the one hand due to their illness behavior, such as physical inactivity, poor diet, or excessive smoking, and on the other hand due to long-term

medications, which can be associated with all sorts of side effects, such as metabolic syndrome, osteopenia, or osteoporosis. Moreover, thyroid function may be altered after menopause and influence mental well-being. Other frequently occurring medical illnesses are respiratory ailments or cardiovascular problems, especially in women with schizophrenia. Unfortunately, this patient group is at great risk for neglecting their psychiatric as well as their general health needs, and this might especially be a problem in the elderly. Thus, for example, in a study by Lindamer et al. (2003), elderly women with schizophrenia were less likely to have had pelvic examinations and Pap smears or mammograms than women without psychiatric diagnoses. Women of this age group should therefore be carefully monitored regarding their physical health with routine physical checkups, including blood pressure, weight, and laboratory tests (glucose, lipids, etc.), EEG, mammography, and Pap smears.

Conclusions

Menopause is a physiological event but is accompanied by massive hormonal and other biological alterations and often also manifold psychosocial changes. All these changes can obviously trigger or aggravate mental problems and disorders in vulnerable, predisposed women. This has especially been shown in schizophrenic psychoses and depressive disorders.

This enhanced vulnerability around menopause and the manifold interactions between biological and psychosocial risk factors for mental disease in this age group have multiple implications.

In the *clinic*, women in the perimenopause have specific diagnostic and therapeutic needs, and consideration of the menopausal status should be part of standard clinical care for mentally ill women. The appropriate treatment strategy in perimenopausal women should not only consider the use of specific psychotherapeutic and psychosocial interventions but also the potential benefits of estrogen replacement in addition to standard psychiatric care.

The application of estrogens should of course always be decided on the basis of an individual risk-benefit assessment in close cooperation between psychiatrists and gynecologists. It goes without saying that the final decision has always to be made by the woman herself after thorough information. Preferably the decision should also be based on additional nonpsychiatric indications.

Although many promising studies suggest that the neuroprotective properties of estrogens justify their use as an adjunctive strategy to traditional psychopharmacological therapies, further *research* in this age group is needed, especially regarding schizophrenic psychoses. This means more research on indications and contraindications of estrogen replacement for women in the perimenopause who are at risk for or suffering from mental disorders, especially also on the relative risks of hormone replacement as compared to treatment with psychoactive drugs or on the best augmentation strategies. We also need more research on specific psychotherapies and alternative treatment strategies in the perimenopause.

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