SPECIAL ARTICLE

The unique challenges of managing depression in mid-life women

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Throughout most of their lives, women are at a greater risk of becoming depressed than men. Some evidence suggests that this heightened risk is associated with increased sensitivity to the hormonal changes that occur across the female reproductive lifecycle. For some women, the peri-menopause and early post-menopausal years may constitute a "window of vulnerability" during which challenging physical and emotional discomforts could result in significant impairment in functioning and poorer quality of life. A number of biological and environmental factors are independent predictors for depression in this population, including the presence of hot flashes, sleep disturbance, history of severe premenstrual syndrome or postpartum blues, ethnicity, history of stressful live events, past history of depression, body mass index and socioeconomic status. This paper explores the current knowledge on the complex associations between mood changes and aging in women. More specifically, the biological aspects of reproductive aging and their impact on mood, psychosocial factors, lifestyle, and overall health are reviewed. In addition, evidence-based hormonal and non-hormonal therapies for the management of depression and other complaints in midlife women are discussed. Ultimately, this article should help clinicians and health professionals to address a challenging clinical scenario: a preventive and effective strategy for the management of depression in the context of the menopausal transition and beyond.

Key words: Depression, menopause, symptoms, hormones

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Depression in mid-life women is a significant cause of morbidity and disability (1). The unique manifestations and multifactorial etiology of mid-life depression makes it difficult to recognize and treat (2). In addition, symptoms of depression may overlap with those associated with menopause, presenting a clinical dilemma for psychiatrists and other health professionals in women's health (3). As the baby-boomer generation of women approaches and passes menopause, mid-life depression has become a serious public health issue and the subject of interest of a growing number of epidemiological and clinical studies.

This paper examines the evidence for and the nature of relationships between mood symptoms and aging in women, including chronological and reproductive aging, and between mood symptoms and other psychosocial, lifestyle, and health factors. In addition, the biological basis for development of depressive symptoms in mid-life women, and the potential for hormonal and non-hormonal therapies to provide relief, are discussed.

MOOD, MID-LIFE AND MENOPAUSE

Mid-life women may seek medical advice due to such symptoms as hot flashes, aches and stiff joints, trouble sleeping, and lack of energy. In the Melbourne Women's Mid-Life Health Project (4), some of these symptoms were experienced at baseline by more than 40% of the 438 women surveyed in the late stages of the menopausal transition. Of particular interest, nervous tension and feelings of downheartedness and sadness were among the six most common complaints.

The causal relationships between depressive symptoms and menopause, however, are unclear; a particular controversy has been established around the question whether depressed mood is caused by psychological factors related to aging or whether ovarian hormonal changes may play a significant role in its occurrence.

Research on the relationship between menopause and depressive symptoms has provided contradictory results. Several studies revealed no relationship (5-7), while others found that mood symptoms decreased with increasing age (8), or that there was an increase in depression among women in the menopausal transition (9). Controlling for the presence of vasomotor symptoms reduced the correlations between depression and menopause in some reports (10). A strong relationship was found between hysterectomy and depressed mood (11).

Longitudinal studies that followed subjects through the transition from regular menstruation to the post-menopausal period have provided contradictory results as well. Different methodologies and the confounding effect of chronological aging make the results of these studies difficult to compare. In addition, correlations between changes in ovarian hormones and mood are not clear, because few studies measured these parameters. Some longitudinal studies have shown no relationship between depression and menopause (10,12). Other studies demonstrated an increased risk of depression during the transitional phase from peri-menopause to post-menopause (13,14); in particular, women entering this transitional phase earlier had a significant risk of developing new-onset depression (15). Dennerstein et al (12) found both an improvement in mood during mid-life and a decrease in negative mood as menopausal symptoms improved.

Reproductive aging in women has been divided into stages by the Stages of Reproductive Aging Workshop (STRAW) consensus (16). A recent restaging study (17) has used data to provide clinicians with practical definitions of the stages of the menopausal transition. Irregular menses, defined as more than 7 days difference persistently occurring between the length of cycles, is characteristic of the early menopausal transition, which begins at about age 35. The late menopausal transition begins when there have been at least two missed menstrual periods, and the post-menopause is the period which begins after the last menstrual period. The Melbourne Women's Mid-Life Health Project study showed that estradiol levels varied widely early in the menopausal transition, with a dramatic decrease in the late menopausal transition period, while follicle-stimulating hormone (FSH) increased (18). After the final menstrual period, estradiol levels continued to fall and FSH continued to rise.

The occurrence of physical and mental symptoms in women during menopausal transition stages was documented in the Women's International Study of Health and Sexuality (WISHeS), a large cross-sectional survey of women aged 20 to 70 years in France, Germany, Italy, the United Kingdom, and the United States. Subgroups of women at several stages were prospectively defined, and symptoms in physical, vasomotor, psychosocial and sexual domains were evaluated (19). Regularly menstruating women aged 20 to 49 were compared with post-menopausal women aged 50 to 70 and also with women who had surgical menopause before and after age 50. Subjects with surgical menopause were of interest because oophorectomy removes approximately half of circulating androgens, as well as estradiol, and the effects are more severe and sudden than naturally occurring menopause (20).

This important study showed that some symptoms experienced by mid-life women were clearly related to declining estradiol, including vasomotor symptoms, poor memory, trouble sleeping, aches in the neck/head/shoulder area, vaginal dryness, and difficulty with sexual arousal. These symptoms reached a maximum prevalence at age 50 and occurred earlier in women who had early (before age 50) surgical menopause. There was a curvilinear effect of age, and there were no differences between women from different countries and no effect of body mass index on the prevalence of this group of symptoms (19).

In contrast, psychological symptoms, such as mood swings, and breast pain showed a curvilinear pattern that peaked much earlier at age 35 to 40 years, or during the early menopausal transition period. After age 35 to 40 years, mood symptoms decreased with age through menopause and into the post-menopausal period and were increased in the presence of other physical or mental health problems. Interestingly, significant differences were found between women from different countries in the prevalence of this group of symptoms (19).

A third cluster of symptoms was also observed that did exhibit a linear effect of age with no maximum prevalence at age 50. These symptoms, such as decreasing physical strength and lack of energy, are the expected effects of increasing age and were also affected by the country of origin, body mass index, and other physical and mental problems (19).

Similar results were found in the Melbourne Women's Mid-Life Health Project, in which positive and negative moods, as well as hormone levels, were followed in a longitudinal fashion. Depressed mood declined significantly with aging. The results also showed that being in the menopausal transition phase amplified the negative mood effects of other major life events, such as poor health or job loss (12).

These observations suggest that the menopausal transition may be considered a "window of vulnerability" during which women are at high risk for depressive symptoms. This vulnerability period is similar in nature to other well-known vulnerability phases, such as the premenstrual period and the immediate post-partum period. The Melbourne Women's Mid-Life Health Project investigators found several risk factors associated with depression during the menopausal transition. A previous history of depression or premenstrual tension, negative attitudes about menopause, as well as lifestyle and psychosocial variables, were important risk factors for depressive symptoms (12). In addition, a follow-up study 11 years later of women aged 57 to 67 found that depression was highest for those who had surgical menopause and for those who were still menstruating (11).

In another substudy, happiness scores during and after the menopausal transition were followed and found to be significantly related to happiness scores recorded before the transition began. Before and after the menopausal transition, happiness scores were the effect of intrinsic personality factors and extrinsic factors, such as marital status, work satisfaction, and life events (21). In general, well-being increased over time as women passed through the menopausal transition, and no direct effect of hormone levels could be ascertained (22).

Another area of interest was the effect of the "empty nest syndrome" on mood symptoms for women in the menopausal transition. This substudy of the Melbourne Women's Mid-Life Health Project showed decreases in depressed mood and daily hassles with increases in positive mood and well-being associated with the "last exit event", when the last child left home. Interestingly, the return of children to home during the menopausal transition resulted in reductions of positive mood and decline in the frequency of sexual activity for women (23).

The consequences of physical, emotional, or sexual violence on mood in mid-life women were also evaluated. This substudy of the Melbourne Women's Mid-Life Health Project showed that intimate partner violence predicted depressed mood, divorce or separation, low sexual functioning, and use of psychotropic drugs (24). Among the overall population, 22% had used psychotropic drugs, most often antidepressants. Four percent had had psychiatric hospital admissions and 7% had had counseling. Psychotropic drug use was associated with interpersonal stress, poor self-ratings of health, and premenstrual depression (25).

Structural equation modeling has been used to show the relationships between changing estradiol levels and the symptoms specifically associated with declining estradiol levels. Women's sleep and perception of health are affected by vasomotor symptoms. Poor lifestyle choices, daily hassles, and stressors also affect mood. Also, decreases in estradiol compromise mood by affecting sexual functioning and women's feelings for partners (26).

IS TREATMENT FOR DEPRESSION DIFFERENT IN MID-LIFE WOMEN?

Chaotic changes in hormone levels during the menopausal transition may be one of the major factors in increased risk of depression (27-29). Clinicians have an opportunity to provide a targeted therapy in the form of a stable hormonal milieu, which may exert a prophylactic and/or neuroprotective effect to prevent depression, as well as a therapeutic effect (29,30).

An ongoing longitudinal study, the Harvard Study of Moods and Cycles, reported on the long-term, prospective evaluation of 1000 women who were pre-menopausal (36 to 44 years of age) at the time of enrollment. They received periodic hormonal, psychiatric, and quality of life assessments, and the results were controlled for factors that are commonly investigated in depression, such as body mass index, smoking, marital status, and occupational status. The data from this study indicate that peri-menopausal women were two times more likely than premenstrual women to develop new-onset severe depression. In addition, the risk was exacerbated in those who developed vasomotor symptoms during peri-menopause (15).

This study indicates that peri-menopause and vasomotor symptoms, caused by estrogen fluctuations, may have a common biochemical pathway with depressive symptoms. The history of estrogen research provides ample evidence to support a strong role for estrogen in regulating brain function. Neuroprotective effects and a role in preserving memory and cognition are well documented, as are thermoregulatory and antidepressant effects in animal and clinical studies. The brain regions most likely to be affected by estrogen are those more likely to be related to monoaminergic systems, including the serotonergic and norepinephrine systems (31), and other evidence supports the role of estrogens in synthesis, release, and receptor activity of serotonin and norepinephrine (32,33). Consequently, it is intuitive to believe that the absence or intense fluctuation of estrogen could result in mood and behavioral changes, as well as vasomotor and other menopausal symptoms.

Several controlled clinical studies examined whether estrogen therapy may have an antidepressant effect in peri-menopausal and post-menopausal women with major depressive disorder (30,34-37). An important finding of these studies was that estrogen was not efficacious for depression in post-menopausal women, suggesting that fluctuating estrogen levels, rather than absolute estrogen levels, may be more important for the antidepressant effects of estrogen. Another interesting aspect of these studies was that positive results were associated with use of transdermal rather than oral estrogen. This finding may be due to the heightened bioavailability of estradiol with transdermal administration, which could be advantageous for the interaction with estrogen receptors in brain areas that regulate mood and behavior.

Another point for consideration in treatment of depression in mid-life women is the efficacy of antidepressant therapies for relief of physical symptoms of menopause, such as hot flashes. A set of prescription data collected by McIntyre et al (38), before and after publication of negative results concerning the use of hormone replacement therapy from the Women's Health Initiative in July 2002 (39), may be relevant to this question. The initial reports of the Women's Health Initiative study suggested no protective effect against (actually, a slightly increased risk for) cardiovascular events (e.g., stroke, myocardial infarction) among post-menopausal women using hormone therapies. As a result, physicians became more reluctant in prescribing estrogen, even for younger, symptomatic women. The study by McIntyre et al (38) demonstrated that hormone replacement therapy prescriptions decreased in the year following the Women's Health Initiative results; interestingly, the number of prescriptions for antidepressants significantly increased, suggesting either that women developed psychological symptoms (e.g., depressive symptoms, anxiety) as they stopped using estrogen or that antidepressants were being used to treat menopause-related symptoms. Limited comparisons of estrogen and antidepressant therapies for treatment of depression in women with menopausal symptoms have indicated similar efficacy of escitalopram (40) and hormone therapies for relief of menopausal symptoms and improvement in menopause-related quality of life measures. Duloxetine (41) and citalopram (42) open trials also suggest that antidepressants may have a positive impact on menopausal symptoms, an important treatment consideration for women who cannot or will not take estrogen.

Other point of interest is whether age and menopausal status of mid-life women could affect the efficacy of some antidepressant therapies. Several clinical trials have shown differences between the responses to antidepressants of pre- vs. post-menopausal women (43) and younger vs. older women (44-47). In a pooled analysis, responses to selective serotonin reuptake inhibitors (SSRIs) appear to be affected by age (i.e., higher in women younger than 50 years of age than in women older than 50 years), whereas responses to venlafaxine, a serotonin-norepinephrine uptake inhibitor (SNRI) were similar across age groups (48).

The question of whether estrogen plays a role in this difference in efficacy was investigated in a pooled analysis of data from women over 50 years of age who were or were not receiving concomitant estrogen therapy during treatment with SSRIs or venlafaxine in eight studies. This study showed higher response rates to venlafaxine than SSRIs in both

groups. However, the gap in efficacy between SSRIs and venlafaxine was significantly larger in women who did not receive estrogen therapy, and SSRIs were significantly more effective than placebo only in the women who received estrogen (48). These data support previous evidence that estrogen might modulate or prime binding affinity/response to SSRIs (49).

The emergence of vasomotor symptoms in mid-life women is hypothesized to be the result of disturbed thermoregulatory function, a complex, hypothalamus-based process. As estrogen levels fluctuate, the so-called thermoneutral zone becomes significantly narrowed, leading to frequent sweating or shivering in response to normal changes in body temperature and producing the characteristic heat dissipation of menopause (50). Thus, the treatment for hot flashes aims to restore/expand the thermoneutral zone and consequently keep the changes in body temperature within that zone.

Although estrogen remains the gold standard for treatment of vasomotor symptoms, several alternative therapies, including many natural remedies, have been investigated. These include psychoactive medications, such as antidepressants, mood stabilizers, anticonvulsant medications, and anti-anxiety therapies (51-58). It should be pointed out that two of the most popular natural remedies for vasomotor symptoms, soy and black cohosh, have been found to have very little impact on these symptoms when compared with placebo in controlled trials (59) and that women may still be exposed to adverse events and side effects through their use.

Another strategy for women with significant nocturnal vasomotor symptoms (night sweats) would be to improve sleep patterns. A trial of the sleep agent eszopiclone for menopausal women with insomnia and awakenings due to hot flashes was recently shown to have a positive effect on these symptoms. The treatment also promoted improvement of mood and quality of life, possibly due to improved sleep patterns (60).

CONCLUSIONS

Epidemiological and clinical studies demonstrate that mood changes and depressive symptoms may occur in some women during the menopausal transition. This period of fluctuating hormone levels constitutes a "window of vulnerability" for depression, especially for women with a previous history of depression or for those with concomitant, severe menopausal symptoms. Estrogen fluctuations may affect mood changes indirectly, through mediation of menopause-related physical symptoms, particularly sleep and sexual disturbances. In addition, estrogen may affect both vasomotor and depressive disturbances through common biochemical pathways and receptor-mediated actions on brain function.

Estrogen therapy has been shown to improve both mood and vasomotor symptoms and remains a viable option for symptomatic mid-life women. Recent concerns involving the long-term safety of estrogen therapy have led clinicians to pursue non-hormonal treatment strategies. Low-dose antidepressant therapy has been shown to improve vasomotor symptoms as well as depression and may be the preferred alternative for women with depression who cannot receive estrogen. Clinical evidence also supports use of some anticonvulsant and anti-anxiety therapies, as well as sleep agents, for treatment of hot flashes. Natural remedies in general have not shown a positive impact on vasomotor symptoms.

We conclude that, although depression in mid-life women presents unique challenges due to the added complexity associated with the menopausal transition, the "window of vulnerability" for depression also constitutes an opportunity to provide targeted and effective therapies that address both physical and mood symptoms in mid-life women.

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