EDITORIAL

Shifting Paradigms About Hormonal Risk Factors for Postmenopausal Depression

Age at Menopause as an Indicator of Cumulative Lifetime Exposure to Female Reproductive Hormones

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The article by Georgakis et al in this issue of *JAMA Psychiatry*[1] is a meta-analysis of 14 observational studies addressing the association of depression after menopause in women with both age at menopause and duration of the reproductive period. Age at menopause is used to estimate the duration of the reproductive period because there is less variability in the age range for menarche (within a 3-year window in 80% of girls)[2] than for menopause (within a 7-year window for approximately 80% of women).[3] The meta-analysis concludes that there is a small but statistically significant increased likelihood of depression after menopause that is inversely associated with increasing age at menopause (odds ratio [OR], 0.98, in 13 studies) and increasing duration of the reproductive period (OR, 0.98, in 5 studies), which is defined as age at menopause (defined as 1 year after final menstrual period) minus age at menarche. This translates to a 2% reduction in risk for each 2-year increase in menopausal age. Therefore, the older a woman is at the time of ovarian senescence and the greater the number of years between the age at menarche (first menses) and at menopause (defined as final menstrual period or 1 year after final menstrual period), the lower the risk that she will experience depression in her postmenopausal years.

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Population-based studies show that the median age at the final menstrual period is 52.5 years, and 90% of women have their final menstrual period by age 56 years.[3] The vast majority of the articles included in this meta-analysis were conducted in women whose average age was 55 years or older; the average age was 60 years or older in half of the studies. In addition, the average age for women in most studies was at least 5 years older than the average age at menopause that they reported. Therefore, this meta-analysis does not address depression associated with the gonadal steroid fluctuations of the perimenopause or recent estradiol withdrawal of the immediate postmenopause. Rather, the analysis applies to depression in older women whose brains have not recently been exposed to estradiol or other reproductive hormones and for whom hormonal risk factors have previously been considered less relevant.

Results of this study provide a novel paradigm for understanding the potential impact of central nervous system (CNS) exposure to female reproductive hormones and depression. The implication is that prior and cumulative exposure to hormones has a sustained impact on the brain, increasing vulnerability to depression years after these exposures. To date, most studies linking reproductive hormones to mood disturbance have conceptualized the association as concurrent or proximate. That is, the brain is concurrently or recently exposed to changes in reproductive hormones that provoke an adverse mood response in susceptible women.[4] This concept derives from observations that mood changes occur during the immediate postpartum period when levels of estradiol and progesterone fall rapidly, during the premenstruum when mood deteriorates in the context of fluctuating levels of estradiol and progesterone over the previous month, and during the perimenopause, when levels of estradiol vary widely. Other neural diseases linked with hormonal exacerbations (eg, catamenial epilepsy, migraines in pregnancy) are based on a similar temporal construct. Animal studies have demonstrated that estradiol rapidly regulates neural activities through genomic and nongenomic processes. Such observations provide a mechanistic basis for the potential rapid neuromodulatory and neuroprotective effect of estrogens on mood. Related to this concept is that the underlying hormonal milieu influences the impact of female hormonal changes on mood. Clinical trial data showing that estrogen therapy improves mood in depressed perimenopausal,[5] but not postmenopausal,[5] women suggest that depression in postmenopausal women is not hormonally sensitive.

In contrast to the acute effects of reproductive hormones on mood in cycling women, the article by Georgakis et al highlights a potential neuroprotective effect of gonadal steroids on mood that is delayed and extends into the stable hypoestrogenic and hypoprogestinemic environment of the postmenopause. Other nonpsychiatric diseases in postmenopausal women have similarly been linked with earlier age at menopause. These include a greater risk for cardiovascular disease, cognitive decline, and dementia among women who had an artificially early surgical menopause or an earlier natural menopause. The current article adds postmenopausal depression to that list, with findings that show similarly that the effect of a slightly early natural menopause is small, while the effect of premature menopause is much stronger. Mechanisms underlying the neuroprotective effect of an older age at menopause are not fully elucidated and may vary between dis-

ease end points. Prolonged exposure to endogenous estradiol during the reproductive years certainly has cardiovascular and neurovascular benefits, but these effects are challenging to disentangle from the potential benefits of end-organ exposure to predictable fluctuations of estradiol across the cycle, intermittent progesterone exposure after ovulation occurs, or its neurosteroid metabolites (eg, allopregnanolone).[6] Alternatively, increasing duration of hypoestrogenism and hypoprogestinism between an earlier menopause and the onset of depression with increasing age may result from an increased opportunity for depression.

Of note, studies of reproductive hormone effects in the brain assume that systemic levels of female reproductive hormones are a reliable proxy for CNS levels and that CNS levels are comparable throughout all brain regions. However, evidence supporting this key assumption is limited. For example, CNS levels of the enzyme aromatase vary among cortical regions.[7] As a result, estradiol can be produced tonically from steroid precursors in some brain regions at levels sufficient to generate estradiol's neuroprotective effects rather than relying solely on widely varying levels of ovarian estradiol production. Other indirect mechanisms that may confer risk for subsequent depression include persistent perturbation of the hypothalamic-pituitary-adrenal axis, similar to the impact of early life stress on the hypothalamic-pituitary-adrenal axis, which precedes and increases the risk for later onset of depression.

A significant limitation of this meta-analysis is that only 2 studies controlled for past depression, the primary predictor of subsequent depression. Other limitations are that (1) the effect is very small, (2) study designs are primarily cross-sectional, precluding determination of the beginning of mood disturbance, (3) depression is defined primarily using self-reported scales that measure depressive symptom burden rather than a categorical depression diagnosis, (4) age at menopause and menarche are retrospectively self-reported, and (5) women who are either currently using or previously used hormone therapy are included. Use of hormone therapy confounds the analysis because the menstrual marker indicating the timing of natural menopause cannot be distinguished from an exogenously induced withdrawal bleed of hormone therapy with cyclic progesterone. Importantly, the implication that neural effects of reproductive hormones are responsible for the association between these reproductive markers and postmenopausal depression risk does not take into account the many other factors that might confound this association, each of which is independently associated with both risk for depression and earlier menopause. These risk factors include sleep difficulties, stress, functioning in work and relationships, and early-life adverse exposures (eg, socioeconomic disadvantage, childhood maltreatment).

This meta-analysis is a commendable effort to expand thinking about the role of lifetime exposure to reproductive hormones in the occurrence of postmenopausal depression and to shift our research focus to explore a new paradigm. The literature in this area would benefit from prospective studies that investigate the incidence of diagnostically confirmed depression episodes during and after the menopausal transition. Given the small effect size and limitations of the studies used in this analysis, more direct evidence supporting a sustained and delayed neuroprotective effect of extended exposure to estradiol, cyclic progestins, and their neurosteroid derivatives is required to support use of hormonal therapy as a therapeutic approach to protecting against postmenopausal depression.

ARTICLE INFORMATION

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