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Estradiol Modulation of Monoamine Metabolism One Possible Mechanism Underlying Sex Differences in Risk for Depression and Dementia

C. Neill Epperson, MD, Deborah R. Kim, MD, and Tracy L. Bale, PhD

Department of Obstetrics and Gynecology, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Epperson); Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Epperson, Kim); School of Veterinary Medicine, University of Pennsylvania, Philadelphia (Bale)

Sex differences in the timing of onset, prevalence, and clinical course of neuropsychiatric and substance use disorders provide clues to the underlying pathophysiology of these disorders. Disorders that occur more frequently in males tend to be neurodevelopmental in nature and include attention-deficit/hyperactivity disorder, autism, Tourette syndrome, oppositional defiant disorder, and, arguably, schizophrenia. The sexually dimorphic organizational effects of androgens for this sex-specific vulnerability. In contrast, it is not until puberty that the sex bias for affective disorders in females is revealed, coinciding with the timing of activational effects of gonadal steroids. From puberty until postmenopause, females are approximately twice as likely as males to have affective and anxiety disorders such as major depressive disorder (MDD), dysthymia, generalized anxiety disorder, panic disorder, and posttraumatic stress disorder. Risk for dementia, particularly Alzheimer disease, is also greater for aging women, although females are relatively protected from early-onset Parkinson disease.¹

Importantly for women, the dynamic fluctuating course of gonadal hormones and neurosteroids, which are necessary for reproduction, unmasks a vulnerability to affective disorders in a sizable subgroup of women. Large epidemiologic studies indicate that 3% to 5% of women experience premenstrual dysphoric disorder, and the risk for MDD increases 2- to 5-fold during the transition to menopause and declines in the years following the final menstrual period.^{2,3} Similarly, endocrine challenge studies indicate that some women are particularly vulnerable to negative affect when exposed to and withdrawn from pregnancy levels of estradiol and progesterone.⁴ Numerous investigations have interrogated, with variable success, the underlying neuroendocrine contribution to the sex bias in affective disorders and some women's proclivity for negative affect during endogenous or exogenous hormonal fluctuations or manipulations. As with many neuropsychiatric conditions,

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Corresponding Author: C. Neill Epperson, MD, Departments of Psychiatry and Obstetrics and Gynecology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104 (cepp@mail.med.upenn.edu).

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identification of biomarkers for potential risk for affective disturbance at reproductive time points or in general has been elusive.

Estradiol has profound effects on brain chemistry, structure, and function and is trophic for regions such as the pre-frontal cortex and hippocampus that are critical to affect regulation and cognition.⁵ Perimenopause and postmenopause provide a natural laboratory for the study of this hormone on behavior. With the aging of our society and women living at least a third of their lives in the postmenopausal state, determining the long-term health effects of hypogonadism after years of hormonal fluctuations has become a major women's health concern.

In *JAMA Psychiatry*, Rekkas et al⁶ report a study that used carbon 11-labeled harmine positron emission tomography to determine the effects of menopause status and fluctuating estradiol levels on monoamine oxidase A (MAO-A) binding (total distribution volume [V_T]). In addition to modulating serotonin synthesis via regulation of tryptophan hydroxylase type 2 gene expression, increasing serotonin 2A receptor binding, and interfering with extracellular serotonin clearance, estradiol diminishes serotonin catabolism by reducing MAO-A levels, messenger RNA expression levels, and enzyme activity.⁵ Under the direction of Jeffrey H. Meyer, MD, PhD, this group has previously reported greater MAO-A V_T in individuals with MDD, those undergoing smoking cessation, and healthy women in the postpartum state, the latter 2 conditions being frequently associated with increased risk for negative affect if not frank MDD. The focus on MAO-A is of general interest in the field of aging research as MAO-A creates oxidative stress and influences cellular apoptosis, factors that are critical for optimal cognitive aging.

In a sample of 19 young premenopausal women (mean age, 28 years), 27 women of perimenopausal age (mean age, 45 years), and 12 postmenopausal women (mean age, 56 years), Rekkas and colleagues⁶ found a 34% greater MAO-A V_T in the perimenopausal age group compared with the premenopausal age group and a 16% greater MAO-A V_T compared with women in the postmenopausal age group. The increase in MAO-A V_T remained greater among women in the postmenopausal age group compared with premenopausal reproductive-aged women. Interestingly, in the perimenopausal age group there was no significant difference in MAO-A V_T between women who were and were not experiencing significant changes in their menstrual cycle length. However, the tendency to cry, which the authors describe as a common symptom of perimenopause, was correlated with MAO-A V_T .

These data are particularly interesting when considering the lifetime impact of estradiol fluctuations. After puberty, females begin to undergo regular, predictable changes in circulating estradiol levels that are accompanied by progesterone increases in the luteal but not ovulatory stages of the menstrual cycle. Although effects of progesterone on MAO-A V_T were not investigated by Rekkas and colleagues, work in non-human primates suggests that progesterone alone or with estradiol would also decrease MAO-A V_T .⁷

All women who live long enough will become perimenopausal and then postmenopausal, but only a subgroup will experience significant clinical depression. Likewise, the tendency

to cry was not reported equally among the perimenopausal women in the study by Rekkas and colleagues. Clearly other factors contribute to this complex relationship with increased risk of negative affect as well as an age-independent cognitive decline⁸ observed during perimenopause. It is not surprising that menstrual cycle changes indicative of the perimenopausal transition were not required to observe the increase in MAO-A V_T among that age group, as ovarian production of gonadal hormones is known to decline before frank changes in menstrual cycle length are observed. However, other factors must be considered as previous studies indicate that lifelong mood sensitivity to hormonal fluctuations such as those observed in women with premenstrual dysphoric disorder and perhaps postnatal depression predicts the risk for MDD during the menopausal transition. Nonhuman primate research⁵ suggests that lifetime history of stress could have a pronounced effect on the relationship between estradiol fluctuations and MAO-A V_T . Early and long-term stress in the form of social subordination or evidence of stress sensitivity among female rhesus macaques contributes to suboptimal estrogen effects on serotonergic function.⁷ Whether the serotonergic effects of frequent and erratic fluctuations in estradiol level, such as those occurring with perimenopause, are moderated by early life adversity or long-term stress in humans is not yet known but is suspected, and this is a topic of active investigation by our Specialized Center of Research funded by the National Institute of Mental Health and Office of Research on Women's Health.

In summary, the study by Rekkas and colleagues⁶ provides the first clear evidence in humans that perimenopausal and postmenopausal women experience lasting increases in MAO-A activity, which could contribute to an overall age-related decline in serotonin function, oxidative stress, and apoptosis. The importance of these observations among women who have not yet experienced changes in menstrual cycle length highlights the need to consider estradiol treatment early in the menopausal transition before serotonergic function is permanently affected by declining levels of ovarian hormones. Although the risk of MDD declines in postmenopause despite continued increases in MAO-A activity, the risk for dementia endures, suggesting the need to examine MAO-A responsiveness to estradiol and other factors such as stress history throughout the aging process.

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