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by Patricia O. Quinn, M.D.

Special Issues for Women with AD/HD:
Hormonal Fluctuations and Mood Disorders

Over the last decade, work with women and girls with AD/HD has made it increasing clear that they must deal with issues that have not previously arisen in defining or treating the disorder. In addition to coping with the core symptoms that are the hallmark of the disorder, women with AD/HD are frequently subjected to fluctuating hormone levels that further complicate the picture by worsening attention and focus or contributing to co-existing mood and/or behavior disorders. Recent research has confirmed that the brain is a target organ for estrogen and that estrogen’s neuronal effects have functional consequences. Specifically, estrogen has been found to stimulate certain populations of dopamine and serotonin receptors in the brain. At the neuronal synapse, estrogen increases the concentration of neurotransmitters such as serotonin, dopamine and norepinephrine. The cyclical production of estrogen may increase symptoms of AD/HD by down-regulating dopamine activity or contribute to mood disorders as decreasing estrogen levels exert their effects on serotonin.

Estrogen, Mood and other Disorders
For years, marked gender differences have been observed in the prevalence of mood and anxiety disorders. Only recently, has estrogen increasingly been seen as playing a role in the treatment of these disorders. Estrogen appears to blunt anxiety symptoms and autonomic reactivity to stress. Recent studies confirm that estrogen alone may have modest effects as a treatment for major depression and that estrogen patches have successfully lessened psychosis in schizophrenic women. In 1990, Huesy first addressed the issue of hormones and their relationship to AD/HD by noting that girls with AD/HD may have increasingly severe problems with the onset of puberty. He wrote that increased hormonal fluctuations throughout the phases of the menstrual cycle might result in increased symptomatology. With the onset of menses and monthly fluctuations in estrogen states, some young women with AD/HD experience a worsening of their symptoms. Women with AD/HD, by definition, have dysfunction in these neurotransmitter systems of their brain. With estrogen enhancing release of these neurotransmitters at the synapse, one would expect improved functioning in women during high estrogen states, such as pregnancy, and a worsening of func-

Recent research has confirmed that the brain is a target organ for estrogen.
Premenstrual Syndrome (PMS) is a common disorder among women. Studies indicate that up to 75 percent of women report some symptoms of premenstrual syndrome, but only about five percent report symptoms severe enough to interfere with daily functioning. The diagnosis of PMS requires that the symptoms be severe enough to affect a woman’s ability to function at home, in the workplace or in her relationships with others. A thorough medical and psychiatric history and perspective daily rating of symptoms for two months should also be obtained. Disorders such as major depression, anxiety, hypothyroidism and diabetes must also be excluded. Epidemiology is not fully known, but there may be some genetic component. Symptoms of PMS can begin anytime after puberty, but most women don’t seek treatment until their thirties, since PMS seems to women as a woman ages. Ovulation seems to be a key factor, as the disorder is not seen during pregnancy or menopause. In treating women with AD/HD, it has become increasing commonplace for them to experience symptoms of PMS that affect their functioning during the second and third decades. As one woman noted, “At 16, I was just diagnosed with AD/HD. I am taking Adderall and the medication is working, however, I still have severe PMS with irritability, increased impulsivity and sleep problems.” In addition, adolescent girls and young women with AD/HD clinically report a high incidence of PMS symptoms involving mood disturbance. The diagnosis of PMS is usually reserved for women whose symptoms include physical discomfort such as breast tenderness, bloating, headache and minor mood changes. This pattern of symptoms must occur regularly at some time in the cycle after ovulation and last until menses begin. Symptoms can begin at any time, but there must be a symptom-free period during the follicular phase of the cycle. There appear to be several patterns to PMS symptoms. They include:  
• Symptoms begin during the week before menstruation and remit during menses.  
• Symptoms begin at time of ovulation and persist through luteal phase.  
• Brief bout of symptoms around ovulation with symptoms returning during second week.  
• Symptoms begin at ovulation and continue through menses with only a 10-day symptom-free period each month.  
Symptoms arising during these years of perimenopause/menopause include memory problems, mood changes and hot flashes. All of these symptoms are now thought to relate to lack of estrogen activity in the brain. Perimenopause is also a time associated with onset of depression in some women who have no previous history of it. These women report feeling sad, irritable, losing energy, being tired and worried, and having trouble sleeping.  
Dealing with the depression and cognitive deficits associated with perimenopause and menopause, in addition to their AD/HD symptoms, may cause women with AD/HD to become less functional as they enter this phase of their lives. As they report more irritability, tension, dysphoria and lability of mood that seriously interfere with their functioning and relationships. They also report a higher incidence of previous mood disorders and are at risk for developing other psychiatric disorders, particularly major depression.  
In addition to the above diagnosis of PMS or PMDD, women with a continuing mood disorder may report premenstrual magnification of symptoms or emergence of new ones. Some women with AD/HD report that symptoms seem to worsen during the premenstrual period. These women may actually have premenstrual magnification. Women who receive this diagnosis may meet criteria for a superimposed PMS or PMDD, or have a current major psychiatric diagnosis with symptoms that worsen premenstrually. This condition most commonly occurs with mood or anxiety disorders, but could possibly be seen with AD/HD.  
Perimenopause and Menopausal Issues  
Perimenopause is that period of several years when estrogen levels begin to drop, menopausal symptoms start to occur, but menses has not stopped. As estrogen levels fall beginning at perimenopause and into menopause, brain volume in females begins to decline. This atrophy occurs primarily in the hippocampus and the parietal lobe, areas primarily associated with memory and cognition. A similar loss in brain volume is seen in males, but not until around the age of 60. This is probably because male hormones decrease much later and more gradually with age. As a result of the continued conversion of the male hormone testosterone to estrogen, males over 60 have approximately three times more estrogen than females. Estrogen levels may be stabilized in perimenopausal women by the use of low dose birth control pills and transition to hormone replacement therapy (HRT) once periods have stopped.  
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Special Issues for Women with AD/HD

We need to design a more holistic approach for treatment of AD/HD in women at various stages of their lives.

Depression and Estrogen
Shepard states that while there is not an increase overall in the number of women experiencing clinical depression during perimenopause, 80 percent of women report a mild depressed mood during this time. This mild depression may be the result of decreasing neurotransmitters in the areas of the brain rich in estrogen receptors. Falling estrogen levels directly influence synaptic concentrations of specific neurotransmitters, particularly serotonin, which plays a critical role in mood regulation.

Research has shown that blood serotonin levels decrease in postmenopausal women and that hormone replacement can restore them to premenopausal levels. In studies conducted on postmenopausal women, HRT has proven beneficial for the treatment of depression. This has led to the speculation that antidepressant efficacy may differ in perimenopausal and postmenopausal women, and that estrogen enhances the efficacy of some antidepressants. Recent studies confirm that the short-term administration of estrogen replacement alone relieves the symptoms of depression in perimenopausal women. In a study conducted by Peter Schmidt at NIMH and published in the August 2000 issue of the American Journal of Obstetrics and Gynecology, 80 percent of women improved with estrogen patch treatment, including six of seven women who had a moderate-to-large effect on depressed mood in traditional prescribed therapeutic doses. These changes in brain activation patterns were observed in specific brain regions associated with day-to-day memory functions.

Hormones and Stimulant Medication
Cyclical variations of hormones (both estrogen and progesterone) during the menstrual cycle often need to be factored in when it comes to the proper dose of medication. Based on the results of several studies and clinical reports, it would seem that adolescent girls and adult women may require different stimulant dosing depending on the phase of their menstrual cycle.

Several studies have now documented that women receiving hormonal therapy performed significantly better on cognitive testing. A recent meta-analysis of 17 randomized studies revealed that women with premenopausal symptoms who received hormone replacement therapy improved verbal memory, vigilance, reasoning, and motor speed. Estrogen was also shown to enhance both short- and long-term memory and the capacity for learning new associations.

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Recent studies confirm that the short-term administration of estrogen replacement alone relieves the symptoms of depression in perimenopausal women.

Definitions and Discussion

Depression—Depression affects brain processes that control movement, emotional response, and the ability to experience pleasure and pain. 1

Serotonin—Serotonin plays a major role in emotional disorders such as depression, suicidal impulsive behavior and aggression. Serotonin is normally involved in temperature regulation, sensory perception and mood control. 2

Norepinephrine—Also called noradrenaline, norepinephrine is a neurotransmitter that doubles part-time as a hormone. As a neurotransmitter, norepinephrine helps to regulate arousal, dreaming and moods. As a hormone, it acts to increase blood pressure, constrict blood vessels and increase heart rate. 2

Luteal Phase—That phase of the menstrual cycle after ovulation and preceding menses. Usually associated with the increase of progesterone and a gradual decline in estrogen levels

HRT—Hormone Replacement Therapy usually refers to the replacement of both estrogen (usually estradiol) and progesterone after menopause. Hormone replacement therapy (HRT) and each women needs to discuss this with her physician before making the decision to undergo HRT. Individualized therapy is recommended as each woman has different needs and risk factors.

Studies of enhanced cognitive functioning seem to indicate that estrogen alone is best and the effects are diminished when progesterone is added. Women with AD/HD will want to discuss this with their physician. It is not recommended that they take the combined HRT, but rather estrogen alone with occasional periods when progesterone is added for 7–10 days every month or every 2–3 months.

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