

AD/HD in Women: Do We Have the Complete Picture? By Patricia Quinn, M.D.

AD/HD affects the lives of millions of women, yet few receive the comprehensive treatment needed to alleviate the impact of its symptoms and optimize functioning. Why is this the case?

First, a significant problem exists for women in obtaining an accurate and comprehensive diagnosis. Repeatedly, women report being misdiagnosed as having a primary depressive illness or bipolar disorder. While these disorders may coexist or share common features of AD/HD, they in no way account for the whole picture in most women. Dealing with undiagnosed AD/HD for a number of years can certainly lead to a degree of demoralization or outright depression, but treating these secondary complications does not get to the root of the problem in these women. To date, the tendency of the medical profession has been to focus on a woman's depressive or bipolar symptomatology and not to look beyond them for the underlying AD/HD.

Second, even if a woman is fortunate enough to be correctly diagnosed with AD/HD, treatment regimes are usually made up of recommendations established as the result of treating elementary school-aged boys. Hormonal fluctuations and the influence of estrogen on the brain are not even considered, much less addressed. No wonder many adolescent girls and adult women with AD/HD report only partial remission of symptoms. In addition, treatment approaches that work for boys with AD/HD may not work for girls or women. For example, when boys' symptoms worsen, it often helps to increase the level of stimulant medication, but this approach frequently fails when applied to women in perimenopause or girls who've started menstruating.

Adele, a case in point: "I was diagnosed with AD/HD at the age of 10. In my history, the severity of my symptoms has at times been mild, and at others rendered me useless. Looking back, it seems as though the severity of my AD/HD symptoms increased during times when my hormones were going through a major change, puberty and after giving birth, for example. I keep wondering if there could be a link? I am now 37 years old and at the very least, perimenopausal. I have gone from being a fun-loving, outgoing person to being very antisocial, wanting to stay home all the time, and feeling very much overwhelmed. Recently, my attention and memory problems seem to be worsening. Sleep does not come easily either, even with medication. My doctor keeps increasing the level of my stimulant medication, but this doesn't seem to help."

The Estrogen Connection

Women with AD/HD must live in their bodies, and those bodies, or more specifically those brains, are subjected to monthly fluctuation of hormone levels. 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, to stimulate a significant increase in dopamine (D2) receptors in the striatum, and to have

effects throughout the brain including midbrain catecholamine and serotonin pathways. For years, marked gender differences have been observed in the prevalence of mood and anxiety disorders. Only recently, has estrogen been increasingly 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. In addition, remission of panic disorder has been observed during pregnancy with improvement noted during each trimester, relapses after delivery, and that breastfeeding can delay this response.

Could this pattern be true for AD/HD in woman, as well? In the following case, a mother reports on her daughter's experience. "I have a 19-year-old daughter who was diagnosed with ADD at age 16. She became pregnant at 17. The curious thing is that all through her pregnancy, and the first six months of breastfeeding, her severe ADD symptoms vanished! She did well during her first semester of college, and she was like a completely different person. However, during her second semester, she began to cut back drastically on the breastfeeding in preparation for weaning her son, and I suddenly realized all her ADD symptoms were returning. Over the next six months, she gradually became the person she was before pregnancy."

This case is not unique. When questioning women, they invariably report that they felt their best and had the least interference from AD/HD symptoms while pregnant. Hussey 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 may result in increased symptomatology. With the onset of menses and monthly fluctuations in estrogen states, some women with AD/HD experience a worsening of their symptoms. The same holds true for menopausal women. Conversely, during high estrogen states such as pregnancy, women report significant improvement.

Low Estrogen States

It has been proposed that whenever brain estrogen levels "fall below the minimum brain estrogen requirement," for whatever reason and at whatever age, brain dysfunction may ensue. Low estrogen states occur prior to menstruation, postpartum and beginning at perimenopause. With menopause, there is an overall 66 percent decrease in estrogen. Symptoms shared by women in low estrogen states include depression, irritability, sleep disturbance, anxiety, panic, difficulty concentrating, and memory and cognitive dysfunction.

PMS, PMDD and Premenstrual Magnification

Studies have indicated that up to 75 percent of women report some symptoms of premenstrual syndrome (PMS). While many women report these symptoms, only about five percent of all women report symptoms that are severe enough to interfere with daily functioning. Symptoms can begin anytime after puberty, but most women don't seek treatment until into their thirties. Ovulation seems to be a key factor, as the disorder is

not seen during pregnancy or menopause. The diagnosis of PMS is usually reserved for women whose symptoms include physical discomfort such as breast tenderness, bloating, headache and minor mood changes. There also appears to be a subgroup of woman (three to eight percent) with PMS whose symptoms are primarily related to mood disorder. These women experience extreme mood and behavioral symptoms, leading to a diagnosis of premenstrual dysphoric disorder (PMDD). These women report symptoms of irritability, tension, dysphoria, and lability of mood that seriously interferes 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. Adolescent girls and women with AD/HD clinically report high incidence of PMS symptoms involving mood disturbance. As one woman noted, "At 36 I was just diagnosed with AD/HD. The medication is working, however, I still have severe PMS with irritability, increased impulsivity and sleep problems." In addition to the above diagnosis of PMD or PMDD, women with a continuing mood disorder may report premenstrual magnification of symptoms or emergence of new symptoms. Some women with a diagnosis of AD/HD report that their symptoms seem to worsen during the premenstrual period. These women may actually have premenstrual magnification. This condition most commonly occurs with mood or anxiety disorders, but could possibly be seen with AD/HD.

Treatment PMS and PMDD

Symptoms of PMS or PMDD have not been found to correlate with any absolute level of estrogen in the blood. Women report symptoms at varying levels of estrogen and symptoms seem to be more related to declining rather than absolute levels of hormones. In addition, anti-estrogen drugs such as tamoxafen and progesterone have been found to stimulate PMS symptoms in susceptible patients. A more recent hypothesis suggests that the problems may not be with the level of estrogen in the blood, but are more likely related to estrogen receptor sensitivities and fluctuating levels of neurotransmitters in the brain. The same receptors stimulated by estrogen are also stimulated by anti-depressant medications in the SSRI family (Selective Serotonin Reuptake Inhibitors). Women with PMS appear to also have abnormalities in blood serotonin levels. Numerous studies have been remarkably consistent in demonstrating that with SSRI treatment, up to 90 percent of women with severe PMS experience almost complete relief of symptoms. These facts suggest that SSRIs work for PMS by increasing the amount of serotonin at the synapse.

Perimenopause and Menopausal Issues

Dealing with the depression and cognitive deficits associated with the decreasing levels of estrogen that arise with perimenopause and menopause, in addition to their AD/HD symptoms, may cause these women to become less functional as they enter this phase of their life. When they report more impairment or increasing symptoms, physicians often respond by increasing the dose of stimulant medication usually with little improvement. Instead, we need to look at all of these factors and design a more

holistic approach for treatment of AD/HD in women during the various stages of their lives.

Depression

Estrogen has proven beneficial in some clinical trials for the treatment of depression, but ineffective in others. This has led to the speculation that estrogen's antidepressant efficacy may differ in perimenopausal and postmenopausal women. Recent studies confirm that the short-term administration of estrogen replacement relieves the symptoms of depression in perimenopausal women.

In a study conducted by Peter Schmidt at NIMH, 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 with major depression, and 19 of 24 women with minor depression.

Cognitive deficits of menopause

Several studies have now documented that women receiving hormonal therapy performed significantly better on cognitive testing. Estrogen enhanced short- and long-term memory, and the capacity for learning new associations. Healthy 65-year-old women who took estrogen also performed better than those without when matched for age, socioeconomic status and years of formal education. Findings suggest that estrogen helps to maintain verbal memory and enhances the capacity for new learning in women. In addition, estrogen has been shown to increase blood flow and brain activation patterns in postmenopausal women prescribed estrogen in traditionally prescribed therapeutic doses. These changes in brain activation patterns were observed in specific brain regions associated with day-to-day memory functions.

The key to better outcomes for women with AD/HD lies not only in better recognition of the disorder, but in the realization that in addition to their AD/HD, they must cope with an ever-changing hormonal environment that can have a significant impact on their AD/HD symptoms. While these symptoms respond equally well to stimulant medication independent of hormone levels, when low estrogen states enter the picture a more coordinated treatment approach may need to be undertaken. For those women whose symptoms worsen during the monthly cycle or with menopause, estrogen administration can help stabilize mood and improve memory. Combined therapy with stimulants, an SSRI and estrogen replacement may be necessary for women with worsening AD/HD symptoms, PMS or PPMS. In addition, estrogen plus stimulants may be necessary to address perimenopausal depression and the cognitive dysfunctions that accompany menopause. While these regimens haven't been tested in research settings for this particular disorder, clinical successes repeatedly validate the wisdom of trying this approach.

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References

Arpels, J.C. (1996). The female brain hypoestrogenic continuum from the premenstrual syndrome to menopause. A hypothesis and review. *Journal of Reproductive Medicine*. 41: 633-939.

Brown, R.T., Abramowitz, A.J., Madan-Swain, A., Eckstrand, D., & Dulcan, M. (1989, October). ADHD gender differences in a clinical referred sample. Paper presented at the annual meeting of the American Academy of Child and Adolescent Psychiatry, New York, NY.

Brown, W.A. (1996) PMS: A quiet breakthrough. *Psychiatric Annals* 26: 569-570.
Castellanos, F. X. (1997) Approaching a scientific understanding of what happens in the brain in AD/HD. *Attention!*, V. 4, #1.

Fink, G., Rosie, R., Grace, O., & Quinn, J.P. (1996) Estrogen control of central neurotransmission: effect on mood, mental state, and memory. *Cell Molecular Biology* 16: 325-344.

Schmidt, P.J. (2000) Estrogen replacement effectively treats perimenopausal depression. *Am J Obstet Gynecol* 2000; 183: 414-420.

Schmidt, R., Fazekas, F., Reinhart, B., Kapeller, P., Offenbacher, H., Eber, B., Schumacher, M. & Freidl, W. (1996) Estrogen replacement therapy in older women: a neuropsychological and brain MRI study. *Journal of the American Geriatric Society* , 44: 1307-13.

Shaywitz, S.E. (1999) Estrogen affects brain activity in postmenopausal women. *Journal of the American Medical Association*. April, 1999.

Sherwin, B., (1996) Hormones, mood, and cognitive functioning in postmenopausal women. *Obstetrics and Gynecology*. 86: 20S-25S.

Sherwin, B., (1997) Estrogen effects on cognition in menopausal women. *Neurology*, 48: S21- 26.

Steiner, and Wilkins, A. (1996) Diagnosis and Assessment of premenstrual dysphoria. *Psychiatric Annals* 26: 571-575.

Tang, M. et al (1996) Effect of estrogen during menopause on risk at onset of Alzheimer's Disease. *The Lancet* 384: 429.

Tiemstra, J.D. and Patel, P. (1998) Hormonal therapy in the management of premenstrual syndrome. *J Am Board Fam Pract* 11: 378-381.

Tivis, Laura J, (1996) Estrogen replacement therapy and cognitive functioning in postmenopausal women. *Menopausal Medicine*. 4: 1-2.

Wickelgren, I. (1997) Estrogen stakes claim to cognition. *Science*. 276: 675-678.