

Ovarian hormones and the female brain: From PMS to menopause

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For many years women have complained of episodic bouts of inappropriate moodiness and depression. Some add insomnia, forgetfulness and flushing to this list. All agree that a sense of well-being is temporarily lost. For the vast majority these symptoms occur during the ten or so days just prior to the onset of the menstrual flow. For others these distressing times only occur in the immediate weeks following delivery of a pregnancy. Some find these episodes tied to the rhythm of their oral contraceptive pill dispenser.

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For most, this cyclic dysphoria ends abruptly during menses with a return to normalcy, a refreshing reprieve for a few weeks until the next cyclic downturn.

For others, however, these symptoms gradually increase both in severity and in duration until the window of recovery is lost. Although worse in the second half of the menstrual cycle, these women complain of a constant low level daily decrease in well-being. Women in the perimenopausal years are like this as their ovaries slowly produce an ever-declining amount of estrogen during the transition into menopause. This era, ranging from the late thirties to the fifties, can be characterized as one in which many women complain of the same symptoms attributed to menopause yet they are still having menstrual periods. The most voiced complaints are memory loss, decreased ability to problem-solve, reduction in vaginal lubrication, inappropriate moodiness and hot flashes. Conventional teaching has been that by definition one cannot be

menopausal and still be having periods. Patients seeking medical help for these perimenopausal complaints are often dismissed as suffering from psychological stress or labeled as neurotic. Many are summarily invalidated as over-imaginative while others are put on antidepressants. It is the plight of women such as these that was immortalized in Gail Sheehy's *Vanity Fair* article and her followup book *The Silent Passage*. The anger and frustration experienced by these patients when the sought-after medical help for their symptoms was not forthcoming led to statements such as “and when they find out how little the doctor knows ... about this standard female transition, they are mad as hell.”

A survey of menopausal women undertaken in 1991 by *McCall's* magazine revealed that in contrast to physician perception, these women were most disturbed by problems with memory and difficulty in concentration rather than hot flashes and night sweats. Once menopausal, the same problems with mood and mental dysfunction seen in the earlier years may become non-cyclic. Depression may now be constant. Daily impairment of memory or reduction in problem-solving may now seriously affect women at their jobs and at home. Whereas once they had the ability to perform two or three separate tasks simultaneously, now full concentration must be given to just one task at a time in order to get things done. Everything must be written down, with reminder notes left everywhere lest day-to-day items be forgotten. The whereabouts of car keys or eyeglasses can become an ongoing daily guess. The stovetop pot left on boil and then forgotten can lead to serious consequences. Add to this that many menopausal women are sleep-deprived as a consequence of night sweats or insomnia and the problems only compound.

In the past three years a partial understanding of these female complaints has begun to emerge. The centers that control sleep, memory, emotion, cognition and regulate temperature are all within the brain. Research data shows that the female brain is a major estrogen-dependent organ. These centers are rich in receptors for both estrogen and testosterone. Estrogen promotes optimal interneuronal

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wiring by increasing the number of synaptic connections between these centers and other parts of the brain. Estrogen also plays a major role in promoting both the receptors for, and production of such brain neurotransmitters, as serotonin, β -endorphins and dopamine. There appears to be great interpatient variation in the optimal level of central nervous system (CNS) estrogen required, but any time this

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Testosterone is said to be utilized in both the emotion centers of the hypothalamus but also in the libido areas of the limbic system. It also promotes a heightened sense of well-being and mental energy which has been characterized at times as female aggressiveness. For testosterone to function maximally, a certain amount of brain estrogen also needs to be present, for the testosterone receptor is thought to be created by estrogen. This may explain why the loss of sexual drive and decrease in orgasmic response seen in many women after chemotherapy for breast cancer is only partially improved by replacing testosterone alone. Their ovaries have stopped secreting both estrogen and androgens due to the chemoablation.

Brain estrogen levels may drop below the minimum CNS estrogen set-point under a number of different conditions. The most dramatic example is after delivery of the placenta when brain estrogen levels may drop suddenly by one-hundred fold. Many feel that the rapidity of the drop is more important than the level of decrease itself. Postpartum depression is now being viewed as a prime example of how estrogen-dependent the female brain is. These mood changes are compounded by the sleep deprivation and stress from the newborn's care requirements. As the new mother's ovaries remain in a state of shutdown by the suppression effect of lactation, she may begin to experience many of the

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same symptoms seen in the postmenopausal woman. These include vaginal atrophy and decreased lubrication, hot flashes, hair loss and bladder irritability with urinary frequency. Eventually the ovaries overcome the suppression, these symptoms resolve and menstrual flow returns. This recovery can be hastened greatly by giving menopausal doses of supplemental estrogen as soon as the patient begins to show signs of needing it. Surgical removal of ovaries in a premenopausal woman has much the same effect as seen in the postpartum state, but since the estrogen levels are not as high as those produced by the placenta, the changes in brain center function occur somewhat less dramatically. It is common to replace estrogen on the day of surgery itself in order to avoid these changes.

Brain estrogen levels may decline due to a decrease in ovarian production, as seen during the perimenopausal years or postmenopause. A relative decline may also occur whenever an anti-estrogen is present in sufficient quantity. Progesterone and tamoxifen are two such agents, both shutting down the estrogen receptor itself. Progesterone may at times also act as an anti-testosterone drug. The dysfunction in mood seen in the premenstrual phase of many women is currently attributed to this anti-estrogen effect. Progesterone, which is made only at midcycle after ovulation, crosses the blood-brain barrier faster than does estrogen. It rises to a peak level seven days before menses begins and creates a significant loss of interneuron wiring plus a drop in neurotransmitters. This is followed by a drop in estrogen itself during the last week of the menstrual cycle which only compounds the unplugging of brain center circuits. It is no wonder that many women express their cyclic premenstrual syndrome (PMS) changes as someone turning down their lights. Most of these patients respond dramatically to low doses of supplementation estrogen started a day or two before their PMS is expected to begin. This extra estrogen raises the overall brain level so that when the progesterone-induced down-regulation occurs, the drop starts from a higher over-all level and therefore

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does not go below the minimum set-point. The medication is stopped on the day the PMS dysphoria would normally resolve. A number of studies have shown that the new antidepressants such as Prozac and Zoloft also help with the cyclic depression of PMS. These drugs help boost already low serotonin levels by blocking reuptake. Estrogen works by increasing total serotonin production as well as promoting circuit rewiring.

The anti-estrogen effect of synthetic progestin can have a negative effect on brain circuits when the birth control pill chosen is a relatively progestin-dominant one. Pills such as Nordette and Loestrin 1.5/30 cause more moodiness and depression than do the more estrogen-dominant pills such as Ortho-Tricyclen and ModiCon. Adding Provera to the estrogen used in the menopausal patient on hormonal replacement therapy (HRT) can have the same effect as did progesterone production during the menstrual cycle. It is not unusual to have a 55-year-old complain that she is experiencing the same unpleasant side effects when she takes her Provera as she did when she was suffering from PMS in her earlier years. Here too adding slightly more supplemental estrogen on the Provera days helps prevent much of the irritability, mental dullness and insomnia. Both endogenous progesterone and Provera can act as a glucocorticoid, thus using a mild diuretic every two or three days may help if bloating or water retention are also problematic.

Clinical trials show that replacing estrogen improves cognition, short-term memory and abstract reasoning in postmenopausal women, even in those who were asymptomatic of hot flashes, insomnia or moodiness. Similar positive effects are being seen when low-dose estrogen is given to women going through the perimenopausal transition. It is now understood that a woman may continue to make sufficient hormones for menstrual cycles to occur, but yet not enough for optimal brain center function. Many of these patients are low enough in estrogen to require a constant daily baseline dose, which is increased during the last half of her cycle to offset the progesterone days. Now those symptoms once attributed by these perimenopausal women to getting older or becoming prematurely senile can be helped greatly.

The future holds promise of even more quality-of-life improvements to come. Preliminary data shows estrogen can reverse or prevent much of the problems with senile dementia. A dramatic 40-60% protection against

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Alzheimer's disease was recently shown by using postmenopausal estrogen replacement. Work is already underway to refine a form of estrogen that will only work once it crosses the blood-brain barrier, thus selectively helping the CNS centers without adding to the rest of the body pool. Finally, estrogen use is having excellent results in treating female cyclic migraine headaches in part due to its ability to modulate serotonin, similar to the mechanism of the new anti-migraine injection Imitrex. ○

Bibliography

Vliet EL, "New Insights on Hormones and Mood," *Menopause Management* 2:14, 1993.

Sherwin BS, "Memory in postmenopausal women: what is the role of estrogen?" *Menopause Management* 9:146, 1993.

Arpels JC, "The Female Brain Hypoestrogenic Continuum From PMS to Menopause: A Hypothesis and Review of Supporting Data," *J Reprod Med* 41:633-639, 1996.