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Depression and Hormones in Women

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Depressive and anxiety disorders have a lifetime risk of 20-26% in women and 8-12% in men. Cultural and psychological variables relating to the role of women may explain some of this difference. Documented risk factors have included childhood trauma/loss, unhealthy coping styles, limited support systems and conflicts in gender roles. The struggle to excel in multiple roles as a wife, mother, friend and sister while working two jobs would be an example of the latter. However this increased risk has been demonstrated in diverse countries and cultures, suggesting that biological variables are significant in addition to cultural/ psychological contributions. Furthermore, depression has been more associated with hormonal transitional events such as menarche, pregnancy, contraceptive use, menstrual cycles, miscarriage, total hysterectomy, perimenopause/menopause and hormone replacement therapies. Thus much of the biological research focus has centered on estrogen and progesterone relationships with known neurotransmitters in the brain.

Estrogen and progesterone should be thought of as brain hormones, not just relevant to ovarian, uterine or bone issues. Receptors for both hormones are found in the amygdala, hippocampus, cingulate cortex, locus ceruleus and raphe nuclei. These areas of the brain comprise critical components of the limbic system that manages the neurotransmitters serotonin, norepinephrine and dopamine. Deficiencies in these neurotransmitters have been associated with a variety of mood and anxiety disorders. Estrogen has been shown to increase neurotransmitter levels, stimulate nerve growth factors and promote neuronal communication via second messenger systems. In other words, estrogen can function as a “fertilizer” of sorts for brain function for many women under normal circumstances. However, normal “circumstances” can become complicated.

Under normal circumstances, estrogen acts as a substantial multiplier of serotonin function by increasing the responsiveness of serotonin receptors and “signal transduction” systems. Thus women would not need as much serotonin as men in order to get the same benefit due to this amplification from estrogen. In fact women do synthesize serotonin at slower rates than men, as a toxic reaction (serotonin toxicity syndrome) could occur if women made serotonin at the same rate as men. This is all fine and good as long as one maintained a significant estrogen level for amplification purposes. In reality, estrogen, progesterone and other hormone levels fluctuate under normal conditions every

month to allow for maximum fertility opportunities. Thus there would be times when estrogen levels would be higher in the first half of the month and declining towards to end of the month. Estrogen levels would also be low during other hormonal transitional periods such as postpartum and perimenopause/menopause. The amplification would be lost then and the individual's serotonin system would have to speed up to compensate. The ability to speed up serotonin and other neurotransmitter functions is felt to be under genetic control. Thus the ability to accelerate serotonin function in response to changes in estrogen function could be impacted by genetic wiring. Someone with a strong family history of depression, anxiety disorder, eating disorder or alcoholism may not be able to speed up their serotonin production enough to compensate for the lack of amplification and become symptomatic.

Estrogen was used as a treatment for depression in the distant past because of these issues. This was abandoned with the Women's Health Initiative study in 2002 – better known as the “prempo study”. This study sought to demonstrate the types of benefits that were afforded menopausal women who took hormone replacement therapy with a combination estrogen/progesterone treatment - prempo. The study demonstrated a higher risk of cardiac disease, stroke, venous thromboembolism and breast cancer in the women treated with prempo. This was especially true for women who had other risk factor such as smoking, lack of exercise, obesity or smoking. The prempo patients did have less colorectal cancer and fewer hip fractures. However this study raised a number of questions about hormone replacement therapy with estrogen/progesterone that has lead to this therapy no longer ranking as a good first line long term treatment. Follow-up studies have demonstrated that the risk of complications were the highest after the age of sixty on hormones. Other studies seek to answer whether estrogen alone (for women without a uterus) would produce similar results. Because of these issues, antidepressants continue to have an important therapeutic role in female depressive states associated with hormone fluctuations (PMS, post-partum and menopausal). Other variables that can be critically important for depressed women include diet, exercise, proper sleep, stress management, the ability to say no, supportive relationships and psychotherapy.