The Effect of Neurosteroids on Depression in Peri-menopausal Women

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Introduction

The purpose of this article is twofold. First, we'll examine the premise that the basic female hormones, 17-beta estradiol and progesterone, with adjunctive use of testosterone and DHEA, are physiologically and neurobiologically imperative for the well-being of the female past midlife. Second, we'll look at the suggestion from our data that dominant mood disorders in midlife women are due to estrogen deficit, rather than estrogen dominance.

Data Review

Serum levels of hormones corroborated with essential amino acid profiles, and Organix® urine profiles, suggesting metabolites of improper catecholamine and other endogenous mood molecules.

The data gathered from our ongoing mood studies strongly suggest that a lack of hormones, most significantly 17-beta estradiol, precipitate decrease of well-being in midlife females. This pattern is acknowledged to exist as a precursor to many degenerative conditions, notably mood and sleep disorders. According to S. L. Berga, key systems mediated by estrogen are the basal forebrain, which regulates attention, and the forebrain cholinergic system, which regulates memory.[1]

The data also show how the up-regulation of GABA at the GABA-A receptor is strongly connected to the down-regulation of progesterone to alopopregnanolone and these processes can be modulated via exogenous administration of transdermal, compounded progesterone.[2]

"GABA and Glycine are known to be the main inhibitory transmitters in the central nervous system acting through ionotropic receptors." This is documented in the work of Bohlen and Halbach on neuromodulators. We link the modulation of the chloride ionic channel to the alpha–4 subunit on the GABA-A receptor, and the impact of progesterone on down-regulation.[3]

Original Four-year Study

In the original study 12 women in late peri-menopause were followed over four years. The original subjects were divided according to emotional and mood evaluations, including our own peri-menopause mood scale. The women were categorized according to primary symptoms of depression or anxiety. The data suggested that women in late peri-menopause prone to anxiety had higher than average levels of 17-beta estradiol (over150 pg/nL) and correspondingly low levels of progesterone (less than 3.3 ng/nL).[4]

Over the following four years of the study the women who were originally high in 17-beta estradiol leveled out over time with exogenous supplementation of transdermal progesterone at doses ranging from 100 mg to 800 mg BID, spaced over the course of a day, to allow maximum uptake.

Over the four years even those women with initially very high levels of estradiol developed symptoms of estrogen deficiency if their estrogen dropped 25% within time frames of four, six and eight months, measured by serum at these intervals. What this means is that the women entering menopause had major tendencies of estrogen deficiency, even if they started out being E2 dominant in earlier peri-menopause. E2 refers to the dominant active estrogen, while estrone E1 is more aggressive. The two share a redux reaction and an electron. So there is an equilibrium reaction but the

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female neuronal networks function on estradiol, which is also referred to as E2, 17-beta estradiol, or estradiol. This is the most important estrogen aspect.

According to Lee Vliet, M.D., and our own data, declining estradiol levels in still menstruating women is the major signal of onset of premenopause; at this point progesterone levels are often still in normal ovulatory range. Our data suggest that many of these women have sub-optimal levels of progesterone for general calmness, and may still need supplementation.[5]

If estradiol has declined to below optimal levels, while progesterone is still functional, then PMS symptoms become much worse. This would seem to contradict the findings of John Lee, M.D., and others, including K. Dalton, who suggested that progesterone was the key to peri-menopausal symptoms.[6]

Our data suggest not so much a blatant contradiction as a lack of full scope observation. Progesterone receptors are made only if there is enough estrogen present. When only progesterone aspects are addressed in a percentage of peri-menopausal women, they do not improve in the long-term. Dalton has stated: "The widespread distribution of progesterone receptors in different target cells explain the numerous different symptoms of PMS."[7]

Our data corroborates what Vliet has asserted, that when women show luteal phase estradiol levels of below 150pg/mL, symptoms set in and may become acute. This is at the second lower peak of luteal phase estradiol when healthy women are at around 200-300 ng/mL around day 20.[8]

The progesterone levels climb normally in both groups; the distinction is the estradiol levels. The data infer that women start to show the most symptoms of estradiol loss when they drop 25% of their original standard level at that same day 20. Usually this correlated with levels of 120-130 pg/mL.

The dominant symptoms that women in their forties and fifties report are fatigue, low sexual energy, lack of motivation and low self-esteem. The accompanying physical symptoms of vaginal dryness and collagen breakdown – when the skin begins to get thin and wrinkled – are consistent with the loss of estradiol.

Menopause

In the last two years 18 women have been followed in the lab and clinically. These women are in active menopause. This means no menstruation for 12 months and/or FSH levels above 20, even if there is some breakthrough bleeding.

Twelve of the women were in definite need of estradiol. Initially the women were given Bi-Est, a combination of estradiol and estriol. The estriol is non bio-active and may have protective effects. The data is clearly suggesting that increases of beta-estradiol have the major impact on mood. All of the women seen were given human identical hormones compounded at The Women's International Pharmacy in Arizona. Transdermal hormones are the preferred method of delivery as receptor sites are readily available and the hormones do not have the "first pass" through the liver, which alters metabolites, particularly of progesterone, but estrogen as well.

Case Report: Peri-Menopausal E2 Dominance and Anxiety

Data were collected on the subject in the first four-year phase of the peri-menopausal study 44 times over four years. The initial data were reported in this journal.[4] The first serum levels indicated 17-beta estradiol levels of 641.8 pg/mL; Progesterone at 5.1. At the time the assessment was made that the subject was showing "estrogen dominance." As our data has evolved, different conjectures have developed. The woman responded very well to higher than usual doses of progesterone applied transdermally. This was compounded at 100mg/g which is equivalent to 1/4 teaspoon. This was used up to six

times a day in luteal phase and often started earlier in month as needed according to her dominant symptom which was irritability/anxiety. Indeed she felt better, for a while. After two years, as she moved closer to menopause other symptoms started to manifest symptoms of estrogen deficit. She called Wallace Simons and the author together and said she was not anxious but flat, almost lethargic, and had developed migraines. Simons said: "You need estrogen, immediately." She responded: "How can I, I'm estrogen dominant!" He responded; "You are not any longer."

The patient was started on transdermal cream estradiol at 1mg/gm and within two hours her headaches and her mood symptoms were alleviated. This correlated with what Simons has been saying for years; when a woman has an estradiol drop of 25% her biology responds and becomes problematic. This woman had indeed dropped from 641 pg/nL down to around 150 at the time of these symptoms, more than a 25% drop. Other women we have been tracking did not have the original high point of estradiol but had more "normal" base perimenopausal levels of around 150 pg/nL in mid luteal phase, dropping to less than 50pg/nL, as they got closer to late perimenopause.

Headaches became a major symptom as in the presence of estradiol, acetylcholine acts as a vasodilator, but without estrogen it becomes vasoconstrictive. Also without enough estrogen serotonin does not access enough receptor sites and so the brain loses the vasoconstrictive effect of serotonin. Many mid-life women bounce between these two types of headaches; vasodilative and vasoconstrictive. It is a question of balance.

According to Edward Klaiber, M.D., in his analysis of many women with treatment resistant depression, there is a correlation between high monoamine oxidase levels and low levels of estradiol and testosterone. This study was conducted at MIT.[9] Monoamine oxidase is a potent catecholamine inactivator. It scavenges serotonin, norepinephrine and dopamine. Dr. Yutaka Kobayashi, a biochemist at the Worcester Foundation and Don Broverman at MIT found a strong statistical relationship between low levels of MAO and high levels of serotonin and testosterone. Klaiber started giving women with a history of treatment resistant depression higher than average amounts of testosterone and estrogen, and the depressions lifted in a very high number of cases.

Conclusion

Today, there are books appearing, not in the scientific press, which fully are consistent with our emerging data but rather, in the integrative or complementary "pop" literature, which are not only misleading but possibly dangerous. Authors, with no medical background, such as T.S. Wiley writing in *Sex Lies and Menopause* suggest that women should take so much estrogen cyclically that they "get their periods again" even after being in menopause for many years.[10] This is based on a false premise which infers that then women will be young and healthy and vital and thin. There is no evidence-based medicine here. One only has to look around at all the women who are still menstruating and their health and endocrine problems are legion; they are not an exemplary group. In fact, if one looks at cultures where women have multiple pregnancies, long periods of nursing and fewer menstrual cycles, there is less female sex steroid related cancer.

According to Wallace Simons, Hargrove, at Vanderbilt University, has stated that there is absolutely no need for a woman to menstruate other than to prepare the uterus for a fetus, as long as there is a healthy but atrophic lining of the uterus.

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