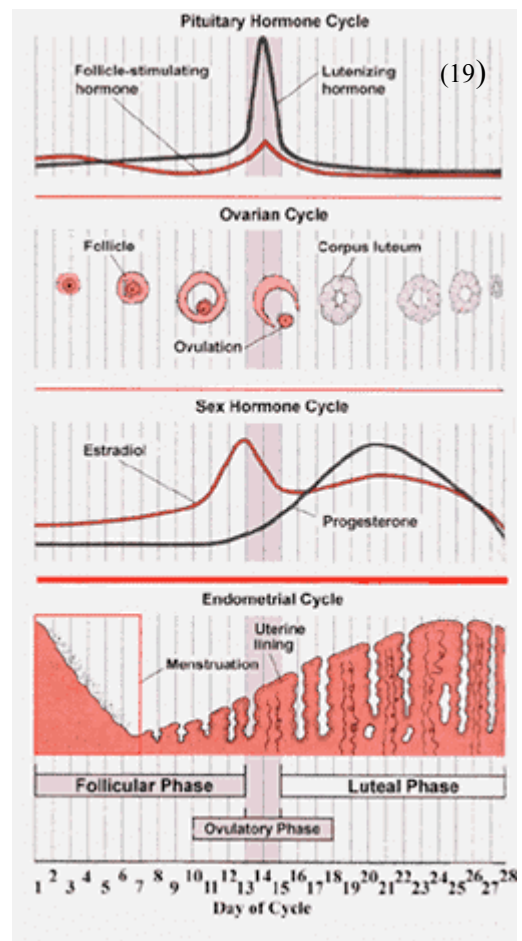


# Fibromyalgia, Chronic Fatigue Syndrome, Female Sex Hormones and Fertility

Robyn M Berent, MBS

Fibromyalgia (FM) and Chronic Fatigue Syndrome (CFS) are illnesses that are characterized by widespread muscle pain, chronic fatigue, sleep disturbances, and other somatic symptoms (1-3). Both FM and CFS are more commonly reported in women, and recently there has been research into the role of female sex hormones with these illnesses (2-6). Young, female patients with fibromyalgia have their first periods significantly later (over age 14) compared to control subjects and patients with other types of chronic pain (7,8). Additional studies found that FM patients have a reduced fertility rate, with a significant number of FM patients having never been pregnant (7,8). It is believed that FM and CFS result from neurohormonal dysregulation in the brain and gonads (ovaries or testes) that perpetuates symptoms, also called the hypothalamic-pituitary-gonadal (HPG) axis (2,3,5). The following review of medical literature will help to elucidate the effect of various female hormones in regards to CFS and FM.

There are several hormones involved that regulate ovulation and menstruation. The start of menses is regulated by the brain, which releases gonadotropin-releasing hormone (GnRH) from the hypothalamus (9). GnRH then acts upon the pituitary gland in the brain to produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (9,10). LH and FSH travels through the blood to the ovaries, where it stimulates the ovaries to ovulate (release egg) and triggers the release of estrogen (the active form is estradiol), testosterone (which is converted to estrogen) and progesterone (a hormone necessary for the maintenance of a pregnancy) (9). This is known as the luteal phase of the menstrual cycle. The presence of these sex hormones decreases the amount of GnRH produced (called a negative feedback loop), and when progesterone and estradiol decrease (called the follicular phase) it causes the hypothalamus to secrete more GnRH (9). As menopause approaches, LH remains high while estrogen production decreases and testosterone increases (which causes the increase in body hair seen in menopause, and also increases the risk of cardiovascular disease). In FM patients, menopause is correlated with increased severity of pain (11). Recent studies have shown there is an



imbalance in some of these hormones with FM and CFS (2-6). Additionally, these studies have shown that there is also a connection to the imbalance of other hormones and neurotransmitters.

Research has already shown that estrogen plays a role in regulating serotonin availability in the brain (4). Serotonin is classically thought of as a neurotransmitter that plays a role in depression, although serotonin is also found systemically and acts upon the gastrointestinal tract, blood vessels, uterus, and others (4). Estrogen increases a cofactor (molecular ‘helper’) that synthesizes serotonin, and also increases the time that serotonin is available in the brain and body (before the serotonin breaks down) (4). As estrogen decreases with age, the serotonin concentration in the body will also drop. Research shows that estradiol does effect pain levels in the brain and spinal cord, and the level of estrogen relates to pain-receptor binding in the thalamus and hypothalamus of the brain (4,6,12). Low estradiol states increased the feeling of pain by inhibiting the function of our endogenous opioids (natural painkillers our own bodies produce), and high estradiol concentrations increased our opioid function (4). One study showed that depressed women had normal levels of hormones, except for estradiol (13). Likewise, FM and CFS women patients are more sensitive to pain during the follicular phase of their menstrual cycle (when there is low estradiol), and men suffer less pain than those women (3,6). Smaller studies involving estrogen had produced conflicting results, with smaller studies showing lower estradiol levels in FM/CFS patients while larger studies found no difference in estradiol concentrations between FM, CFS and healthy patients (2,5).

In addition to estradiol, elevated LH levels have been described in FM patients and normal LH levels in CFS patients (2,3). Higher levels of LH are normally seen in post-menopausal women; however, it is also seen clinically as premature menopause (before age 40), polycystic ovaries, and other conditions that cause infertility (9,10). There are several effects from excessive LH production, such as a decrease in cognitive performance, less self-described depressive symptoms, sleep disturbances and fatigue (2,3,14). LH levels are also significantly higher in FM patients with less depressive symptoms than CFS patients with less depressive symptoms (2). In these studies, all subjects were females who had normal menstrual cycles and were free of birth control pills (2,3). In addition to blood concentrations of LH, the effect of this hormone on pregnancy was examined using animal models. It was determined that increased LH had no effect on egg viability (10). However, the pregnancies of these LH-hypersecreting mice could not be maintained as a result of dysfunctional uterine receptivity (9,10). When the eggs of these mice were transferred into mice that secrete normal amounts of LH, the pregnancy evolved normally and the pups were healthy (10). These results suggest that FM and CFS act differently in regards to LH secretion, and that excessive LH may inhibit correct implantation and gestation of embryos.

LH is a necessary hormone to activate ovaries to produce sex hormones other than estrogen, like progesterone and testosterone. There has been little research into the effect of progesterone or testosterone in regards to CFS and FM. In one large study, the data suggested that progesterone is slightly elevated in FM patients during mid-luteal phase of menses, and the pain threshold for FM patients was modestly related to progesterone

level (15). However, no discussion or observations were made regarding the effects of elevated progesterone in pregnancy. Nor was there any discussion of possible abnormal testosterone break down into estrogen in response to elevated LH in FM patients only (2,3).

**CONCLUSION:** Females state they experience more pain during menstruation and luteal phase of their cycles (11). There is conflicting data regarding the role of sex hormones in the etiology of FM and CFS. Therefore, this examination of research literature suggests that there is not enough evidence that sex hormones play a role in the development of FM or CFS.

Estradiol levels are not affected by CFS or FM, but studies have shown that estrogen does effect the amount of pain one feels (2-6,16). This may explain why there are more women than men complaining of FM or CFS symptoms, or why a lot of FM and CFS women patients are diagnosed during perimenopausal and menopausal states (2-6).

A significant rise in LH levels were found in a subset of FM patients that suffer less depressive symptoms, while there was no increase in any other sex hormones for these patients (2,3). Animal studies have also found that LH hypersecretion contributed to uterine dysfunction in embryo implantation, yet transplantation of the embryo into a normal mouse produced a successful pregnancy (10). However, this result has yet to be confirmed in human subjects. Since LH is produced by the anterior pituitary gland, further research is needed to determine how the pituitary is functioning.

There is no clear answer regarding the effect of other sex hormones in conception and fetal development, specifically progesterone and testosterone. Progesterone was only shown to have an effect on pain levels. Disappointingly, none of these studies examined the testosterone levels in these patients. Normally testosterone is immediately converted into estrogen in the ovaries of reproductive females; however, the possibility of abnormal testosterone production has yet to be addressed. Other studies have shown that an increase in testosterone creates ovarian dysfunction (18). Future studies on these sex hormones may help to elucidate fertility questions in females with FM or CFS.

In case of a confirmed pregnancy, a majority of FM patients experienced a worsening of symptoms during pregnancy and post-partum (11). Since there was no increase in any hormones for CFS patients compared to FM patients, this may suggest that CFS and FM should be treated as separate conditions when facing conception issues. In summation, there is not enough evidence yet to support the idea that sex hormones play a role in the infertility of women with CFS or FM. Yet the animal studies do give hope that their eggs could be transferred into a surrogate in the event of unsuccessful pregnancies by the FM/CFS patients. Further research is needed to clarify these issues.

***Author's Comment:*** *The NNFCN does not endorse any products, and is not liable for any information presented in this article. This literature review was conducted and produced without competing interests or commercial involvement. The information*

*contained in this article is meant to inform patients only. Always consult your physician(s) before stopping or changing any medical treatments.*

#### REFERENCES:

1. Wolfe F, Symthe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P. **The American College of Rheumatology 1990 Criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee.** *Arthritis Rheum* 1990; 33:160-172.
2. Gur A, Cevik R, Nas K, Colpan L, Sarac S. **Cortisol and hypothalamic-pituitary-gonadal axis hormones in follicular-phase women with fibromyalgia and chronic fatigue syndrome and effect of depressive symptoms on these hormones.** *Arthritis Res Ther* 2004; 6(3): R232-238.
3. Gur A, Cevik R, Sarac AJ, Colpan L, Em S. **Hypothalamic-pituitary-gonadal axis and cortisol in young women with primary fibromyalgia: the potential roles of depression, fatigue, and sleep disturbance in the occurrence of hypocortisolism.** *Ann Rheum Dis* 2004; 63: 1504-1506.
4. Rybaczyk LA, Bashaw MJ, Pathak DR, Moody SM, Gilders RM, Holzschu DL. **An overlooked connection: serotonergic mediation of estrogen-related physiology and pathology.** *BMC Women's Health* 2005; 5(12).
5. Cevik R, Gur A, Acar S, Nas K, Sarac AJ. **Hypothalamic-pituitary-gonadal axis hormones and cortisol in both menstrual phases of women with chronic fatigue syndrome and effect of depressive mood on these hormones.** *BMC Musculoskeletal Disorders* 2004; 5(47).
6. Smith YR, Stohler CS, Nichols TE, Bueller JA, Koeppel RA, Zubieta JK. **Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women.** *J Neurosci* 2006; 26(21): 5777-5785.
7. Schochat T, Beckmann C. **Sociodemographic characteristics, risk factors and reproductive history in subjects with fibromyalgia – results of a population-based case-control study.** *Z Rheumatol* 2003; 62(1): 46-59.
8. Raphael KG, Marbach JJ. **Comorbid fibromyalgia accounts for reduced fecundity in women with myofascial face pain.** *Clin J Pain.* 2000; 16(1): 29-36.
9. Mann RJ, Keri RA, Nilson JH. **Consequences of elevated luteinizing hormone on diverse physiological systems: use of the LHbetaCTP transgenic mouse as a model of ovarian hyperstimulation-induced pathophysiology.** *Recent Prog Horm Res* 2003; 58:343-375.
10. Mann RJ, Keri RA, Nilson JH. **Transgenic mice with chronically elevated luteinizing hormone are infertile due to anovulation, defects in uterine receptivity, and midgestation pregnancy failure.** *Endocrinology* 1999; 140(6):2592-2601.
11. Pamuk ON, Cakir N. **The variation in chronic widespread pain and other symptoms in fibromyalgia patients. The effects of menses and menopause.** *Clin Exp Rheumatol.* 2005; 23(6): 778-782.
12. Waxman J, Zatzkis SM. **Fibromyalgia and menopause. Examination of the relationship.** *Postgrad Med.* 1986; 80(4): 165-167, 170-171.
13. Young EA, Midgley AR, Carlson NE, Brown MB. **Alteration in the hypothalamic-pituitary-ovarian axis in depressed women.** *Arch Gen Psychiatry* 2000; 57(12):1157-1162.
14. Casadesus G, Milliken EL, Webber KM, Bowen RL, Lei Z, Rao CV, Perry G, Keri RA, Smith MA. **Increases in luteinizing hormone are associated with declines in cognitive performance.** *Mol Cell Endocrinol* 2007; 269(1-2): 107-111.
15. Okifuji A, Turk DC. **Sex hormones and pain in regularly menstruating women with Fibromyalgia syndrome.** *J Pain* 2006; 11:851-859.
16. Korzun A, Young EA, Engleberg NC, Masterson L, Dawson EC, Spindler K, McClure LA, Brown MB, Crofford LJ. **Follicular phase hypothalamic-pituitary-gonadal axis function in women with fibromyalgia and chronic fatigue syndrome.** *J Rheumatol* 2000; 6:1526-1530.
17. Ostensen M, Rugelsj oen A, Wigert SH. **The effect of reproductive events and alterations of sex hormone levels on the symptoms of fibromyalgia.** *Scand J Rheumatol.* 1997; 26(5): 355-360.
18. Ortega HH, Salvetti NR, Padmanabhan V. **Developmental programming: prenatal androgen excess disrupts ovarian steroid receptor balance.** *Reproduction* 2009; 137(5): 865-877.
19. Holisticonline.com. Menopause and HRT. <http://www.holisticonline.com/images/menstrual-cycle.GIF>