



Hepatitis C HCCAP

Women and Hepatitis: The Estrogen Connection

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Equal Opportunity?

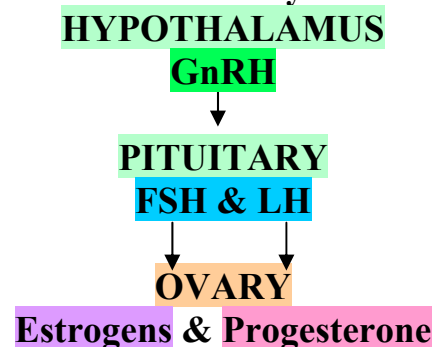
Is chronic hepatitis the same disease in men and women? In two words, the answer is yes *and* no. Hepatitis is primarily a liver disease. Yet, because of the numerous and complex functions of the liver, hepatitis can affect nearly every organ system of the body. Signs and symptoms of hepatitis have been known to manifest in the skin, digestive, nervous, musculoskeletal, cardiorespiratory, urological, immune, and endocrine systems. The production and metabolism of sex hormones are where the symptomatology of chronic hepatitis between men and women diverges. Obviously, the difference is not inherent in the viruses present or in the underlying cause of the disease. The differences in the manifestations of the disease are the result of differences between male and female bodies – the environments in which chronic hepatitis exists. The unique aspects of the hepatitis experience in women are fundamentally the result of the link between the female reproductive system and the liver: the estrogen connection.

Female Hormone Cycles

A hormone is a substance produced in one area of the body that acts on another tissue(s). Hormones are released from the producing organ into the bloodstream for delivery to the target tissue. For menstruating women, the control of the female hormone cycle begins in the brain. A small gland in the brain called the *hypothalamus* secretes a hormone called

gonadotropin-releasing hormone (GnRH). GnRH stimulates the *pituitary gland* of the brain to secrete the hormones *follicle-stimulating hormone* (FSH) and *luteinizing hormone* (LH). FSH and LH act on the ovaries to cause the monthly release of a mature egg. Under the influence of FSH and LH, the ovaries produce *estrogens* and *progesterone*, the female hormones. Figure 1 shows the relationship between the hormones of the female reproductive system. Both estrogens and progesterone are synthesized from cholesterol.

Figure 1: Control of Female Hormone Cycle



Estrogen is a bit of a misnomer as there are actually three estrogen hormones produced in significant amounts by the female body: *estradiol*, *estrone*, and *estriol*. The ovary produces primarily estradiol, the most powerful of the three estrogens. Estrone is also secreted by the ovary but in much lower quantities than estradiol. Most circulating estrone comes from the conversion of estradiol to estrone by the liver. Estriol is the

least prevalent of the three estrogens in a non-pregnant female. Small quantities are produced by the ovary, but most comes from the conversion of estrone and to a lesser extent estradiol. Most of the estrogen in a menstruating woman is produced by the ovaries, but estrogens are also made from precursor molecules in other parts of the body such as fatty tissues, the liver, and the skin. In post-menopausal women and women who have had their ovaries removed, these other locations become the primary producers of estrogens. However, the quantity produced is much lower than that produced by the ovaries.

Estrogens have many functions in the female body. They promote the growth and development of the female reproductive system and breasts at puberty. After puberty, they influence the release of hormones from the brain that control the menstrual cycle. Most of us are familiar with these well-known actions of estrogens, but they have many other effects on the body as well.

Estrogen influences:

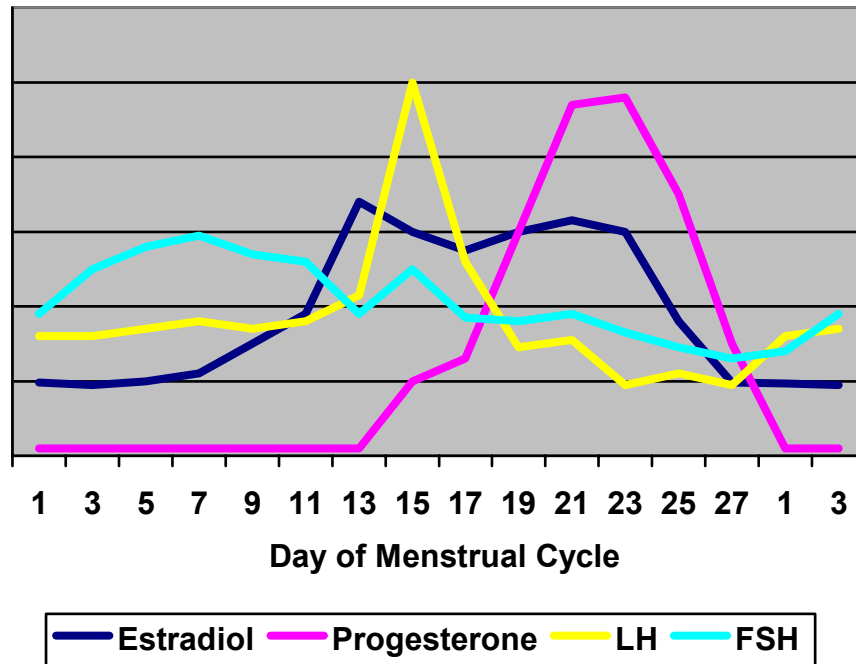
- sex drive
- fluid retention
- protein breakdown in the body
- maintenance and composition of the bones
- brain cell integrity
- blood cholesterol levels
- formation of plaques (blockages) in blood vessels
- skin health
- activity of the intestines
- body temperature
- utilization of sugar

Estrogens are not only metabolized by the liver, they are also inactivated or *conjugated* there. Conjugated estrogens are secreted into the bile. Bile empties into the intestine where conjugated estrogens are reabsorbed into the blood. As blood is filtered by the kidneys, conjugated estrogens pass into the urine where they are eliminated from the body.

Progesterone is the other major female hormone produced by the ovary. Like estrogens, fluctuating progesterone levels regulate the menstrual cycle. Progesterone levels surge after ovulation. It acts primarily on the uterus, making it ready to accept a fertilized egg. Progesterone levels drop if the egg released at ovulation is not fertilized. Dropping levels of progesterone and estradiol initiate the onset of menstrual bleeding. As with the estrogens, the liver is the primary site of inactivation of progesterone.

The control of the menstrual cycle is carefully orchestrated by the body. Figure 2 shows the rise and fall of the major hormones that control and regulate the menstrual cycle according to the day of the cycle. Day 1 is the onset of menstrual bleeding. Day 14 (in a 28-day cycle) is the day of ovulation, when a mature egg is released from the ovary. The day of ovulation varies depending on the length of the menstrual cycle. Anything that disturbs the balance between FSH, LH, estradiol, and progesterone can affect the menstrual cycle.

Figure 2: Hormone Levels in the Menstrual Cycle



Menstrual and Menopausal Symptoms in Women with Chronic Hepatitis

Women in their childbearing years with chronic hepatitis often report menstrual difficulties such as irregular periods, scanty or heavy menstrual flow, and exaggerated premenstrual symptoms including headaches, water-weight gain, irritability, bloating, cramping, and decreased sex drive. Women with cirrhosis have well-documented menstrual abnormalities that are frequently severe enough to cause infertility. Although there have been no definitive studies to correlate the severity of menstrual abnormalities with increasingly severe pre-cirrhotic liver disease, it seems likely that the more severe the liver damage, the more likely it is menstrual abnormalities and symptoms will occur.

Impaired metabolism and inactivation of estrogens in a diseased liver leads to an accumulation of estrogens in the body, and seems to be a likely mechanism for many of

the menstrual symptoms experienced by women with chronic hepatitis. Excessive estrogen disrupts the delicate balance between estrogen and progesterone leading to irregular and abnormal periods.

Other liver-related factors can contribute to menstrual abnormalities. For example, estrogens are known to influence blood protein levels. However, a severely diseased liver may not be capable of responding to this normal signal. The result can be not only excess estrogen but also a failure of the liver to produce proteins that normally bind estrogens. This exacerbates the excess estrogen problem because unbound estrogen is more biologically active than protein-bound estrogen.

As menopause (the end of menstruation) approaches, the ovaries begin to behave less reliably in response to hormonal signals from the brain. During the pre-menopausal (two to five years before menopause) and

menopausal years, some cycles are *anovulatory*, which means an egg is not released. Anovulatory cycles result in lower than normal levels of estrogen and progesterone. However, some cycles are ovulatory. This leads to tremendous variations in the amount of circulating estrogens and progesterone in the body from week to week. Impaired liver metabolism of the sex hormones causes an even more intense and sustained variability in these hormones. This appears to be the primary reason many menopausal women with chronic hepatitis report exaggerated menopausal symptoms such as hot flashes, night sweats, irritability, and emotional lability.

Another link between menstrual and menopausal difficulties and chronic hepatitis is the thyroid gland. Women with autoimmune hepatitis and those with hepatitis C who have been treated with interferon have an increased incidence of thyroid disease. Over activity (*hyperthyroidism*) and under activity (*hypothyroidism*) can occur, although hypothyroidism predominates. Both conditions can cause menstrual abnormalities including irregular periods, scanty periods, temporary loss of periods, and temporary loss of fertility.

Although women with chronic hepatitis have an increased incidence of menstrual and menopausal symptoms, most maintain an active, healthy sex life. Chronic hepatitis should not be an obstacle to a fulfilling, safe sex life. However, be aware that the hepatitis B and C viruses are present in the menstrual blood of infected women. Therefore, the risk of sexual transmission may be increased during a woman's period. Consult your health care providers about safe sex practices appropriate for your condition.

The Good News

While the build-up and faulty metabolism of estrogen in women with chronic hepatitis can cause troublesome problems and symptoms, there is also good news for women with chronic hepatitis. Research studies among people with non-alcoholic, chronic hepatitis have clearly demonstrated that women have less risk of cirrhosis than men of comparable age do. One factor that may contribute to this observation is the level of iron in the liver. A recent study comparing the liver biopsy findings in age-matched men and women with chronic hepatitis C found significantly lower grading and staging among the menstruating women. This finding correlated with the iron concentration in the liver. Further, among the menstruating women in the study, those who were iron-depleted had significantly lower grading and staging than women with normal iron status did.

Estrogen hormones may also protect the liver and slow disease progression. Estradiol is a potent antioxidant, a substance that inactivates chemicals called free radicals that cause scarring and fibrosis. Researchers have found estradiol suppresses liver fibrosis and the activation of *hepatic stellate cells* (HSCs) in animal models. HSCs are believed to be the cells in the liver that facilitate fibrosis and cirrhosis.

The actions of estrogens in the liver are mediated by *estrogen receptors* (ERs) present on the surface of liver cells. Menstruating women have more ERs in the liver than do post-menopausal women and men. The number of normal ERs generally decreases as the severity of liver disease increases. Some researchers have found evidence that the higher concentration of normal ERs in menstruating women may protect against cirrhosis and the development of liver cancer (*hepatocellular carcinoma* or

HCC). Conversely, the presence of genetically damaged or variant estrogen receptors (vERs) seems to correlate with increased risk of HCC. Nonetheless, the role of estrogens in the development of HCC remains somewhat controversial and is an area of active research.

Alcohol, Estrogen, and the Liver: A Bad Mix

While it appears estrogen may offer some protection to women with non-alcoholic liver disease, the effects of chronic alcohol use are more severe in women than in men. Compared to men, women develop alcohol-induced liver disease over a shorter period of time and with less consumption of alcohol. Women are also more likely than men are to develop alcoholic hepatitis and die from alcohol-related cirrhosis. Research in animal models suggests women's increased susceptibility to the liver damaging effects of alcohol is related to estrogen-mediated pathways.

Hepatitis and Pregnancy

Although women with cirrhosis can have impaired fertility, women with less severe liver disease generally retain their fertility. This is important for several reasons. First and foremost, it is important for all women to know their fertility status in order to have the desired control over their reproductive choices. Many women with chronic hepatitis are able to safely conceive and bear healthy children. There appears to be no increased incidence of pregnancy or birth-related complications among women with chronic, non-cirrhotic hepatitis. However, women with chronic hepatitis B or C should work closely with their health care providers to minimize the risk of transmission of the virus to the fetus. The risk of maternal-fetal transmission is around 5% for women with hepatitis C and 10-20% for most women with hepatitis B.

For the majority of women with non-cirrhotic liver disease, it appears pregnancy does not alter the course of disease progression. The exception is women with hepatitis E who can experience worsening of their disease during pregnancy. In addition, there have been some reports of disease flare-ups during pregnancy among women with autoimmune hepatitis. It is unclear if this is due to the pregnancy itself or a lowering of medications during the pregnancy.

Although the hepatitis B and C viruses have been found in breast milk, most experts agree it is safe for infected mothers to breast feed if specific precautions are followed. The infants of women with hepatitis B should be given hepatitis B immunoglobulin and a hepatitis B vaccine within 12 hours of birth. The Centers for Disease Control and Prevention state that if these two shots are given, it is safe for a hepatitis B infected mother to begin breast-feeding. Women with hepatitis C can begin also begin breast-feeding after birth. However, if the nipples are cracked and/or bleeding, most experts recommend expressing the breast milk (if it is possible to do so without contaminating it with blood) and bottle or spoon-feeding it. If this cannot be accomplished, breast-feeding should be temporarily suspended until the nipples have healed. Breast milk will need to be expressed and discarded during this time to maintain milk production. Breast-feeding women should consult their pediatrician if they have cracked or bleeding nipples to determine the safest course of action.

Women with hepatitis C who intend to undergo treatment with interferon and ribavirin must use two forms of contraception during treatment and for six months after completion of treatment. Pregnancy is to be avoided because of the risk of birth defects associated with treatment, especially ribavirin. Men should

follow the same precautions. Women undergoing treatment for other forms of chronic hepatitis should consult their health care providers to determine the potential risk of birth defects associated with their treatment regimen.

All women with chronic hepatitis who wish to conceive should consult with their hepatologist and gynecologist to determine what measures need to be taken to help insure the safety and health of both the mother and child.

Conclusion

Chronic hepatitis presents some unique symptoms and challenges for women. However, as with most challenges, knowledge brings with it a sense of control and choice. If you are struggling with some of the symptoms discussed in this article, discuss them with your health care providers. May you live well.