Introduction

Approximately 1.3 million women in the United States are infected with the hepatitis C virus (HCV). Women differ from men in terms of their risk of cirrhosis and liver cancer, the effects of alcohol on HCV-related disease, and response to HCV treatment. There are also several life issues specific to women that are affected by HCV, such as pregnancy and menopause. This chapter addresses the differences in the HCV experience that specifically affect women.

Risk Factors for Acquiring HCV Infection

HCV is transmitted through blood or blood-contaminated objects. Among persons with chronic HCV infection in the United States, the two most frequent ways the virus is acquired is from use of contaminated needles or other drug paraphernalia, or from receiving a blood transfusion prior to 1992 (when screening of blood for HCV began). Other risk factors for HCV infection are listed in the Table 1.

<table>
<thead>
<tr>
<th>Table 1. Risk Factors for Hepatitis C</th>
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<tr>
<td>Blood transfusion before 1992</td>
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<tr>
<td>Injection drug use</td>
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<tr>
<td>Hemodialysis</td>
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<tr>
<td>Needle-stick injury</td>
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<tr>
<td>Hemophilia</td>
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<tr>
<td>Mother is HCV-infected</td>
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<tr>
<td>HIV infection</td>
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<tr>
<td>Solid organ transplants</td>
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<tr>
<td>Unprotected sex with multiple partners</td>
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Sex with a HCV infected person can be a means of acquiring infection, although the virus is not transmitted very efficiently by sex. Nonetheless, women are at risk of acquiring HCV through their sexual partners.

Studies have shown the following:

- An uninfected woman is more likely to getting HCV from an infected male than vice versa.  

- Women in sexual partnerships with injection drug users are at risk for acquiring HCV in the partnership by engaging in risky injection and sexual practices.

- This increased risk of getting HCV is related to risky behaviors. Women in partnerships with injection drug users are more likely to:
  - Inject drugs with used syringes
  - Allow other persons to inject for them
  - Engage in sexual activities with partners who are injection drug users

- HIV infection increases the risk of acquiring HCV infection by sexual contact.

What Is the Risk of a Woman Transmitting HCV by Sex?

For women infected with HCV and in monogamous relationships, the risk of transmitting the virus to an uninfected partner is less than 1%. Because the risk is so low, it is not recommended that couples specifically change their sexual practices to...
include use of barrier methods. However, this decision will vary with each couple’s comfort level with the predicted risk of transmitting HCV. Additional “common sense” recommendations (since HCV is transmitted in blood) are:

- If sexual activities cause trauma to the mucosa or skin (resulting in blood exposure), use barrier protection or abstain from sex.
- If having sex during menses, use barrier protection or abstain from sex.
- If one or more of the partners has herpes or other open or ulcerating lesions, use barrier protection or abstain from sex.

For women infected with HCV who are not in monogamous relationship, barrier methods should be used. This recommendation also applies to women without HCV to prevent acquisition of sexually-transmitted diseases.

**HCV: Pregnancy and Child-Birth**

**Does Pregnancy Change the Course of HCV Disease in an Infected Woman?**

Whether pregnancy itself has an adverse effect on HCV disease is controversial. Serum aminotransferase levels (ALT) tend to decrease in the first trimester through to the third trimesters and rebound after delivery. These effects may be related to the immune-rebound seen after delivery in other diseases.

For women with more advanced liver disease (such as those with significant bridging fibrosis or cirrhosis), complications of liver decompensation may occur during pregnancy, especially if there is evidence of portal hypertension prior to pregnancy. Women with advanced stages of fibrosis should seek expert medical advice regarding the risks of pregnancy prior to conception. This recommendation is not unique to HCV-infected women but is applicable to all women with chronic liver disease and advanced fibrosis who wish to become pregnant.

**Mother-Infant Transmission of HCV**

The risk of transmission of HCV from mother to infant is approximately 5%. The exact time of transmission is not known. There are no preventative therapies available to interrupt transmission between mother and infant. Mother-infant transmission of HCV is currently the most common mode of acquisition of HCV in children.

**FACTORS ASSOCIATED WITH RISK OF HCV TRANSMISSION FROM MOTHER-TO-INFANT**

- **Presence of HCV RNA in the mother’s blood at the time of delivery.**
  There is no risk of transmitting HCV infection if the mother is HCV RNA negative (even though HCV antibody is present). This provides the rationale for considering treatment of HCV infection in women who are considering future pregnancy.

- **HIV coinfection**
  The risk of transmission of HCV is two to seven times higher in infants born to HCV/HIV coinfected mothers compared to children born to mothers infected with HCV alone. Receipt of HIV antiretroviral therapy during pregnancy may reduce the risk of HCV transmission in coinfected mothers.

**FACTORS THAT MAY BE LINKED WITH RISK OF HCV TRANSMISSION FROM MOTHER-TO-INFANT**

More studies are needed to address this question, but what we know today is as follows:

- **Elevated serum aminotransferase levels in the mother**
  In some (but not all) studies, higher rates of mother-infant transmission are seen in women with higher ALT levels than in those with normal or mildly elevated ALT levels.

- **HCV viral load in the mother**
  Some (but not all) studies show a relationship between high viral load and higher risk of transmission. However, a specific HCV viral load threshold for transmission has not been determined. Longer duration of membrane rupture, invasive fetal monitoring, and volume of blood loss ≥500g during the delivery have been reported as possible factors contributing to mother-infant transmission.
FACTORS NOT RELATED TO RISK OF TRANSMISSION FROM MOTHER TO INFANT

- **Mode of delivery**
  There is much debate about mode of delivery and risk of mother-infant transmission of HCV. The majority of studies report no difference in mother-infant transmission by route of delivery, including studies evaluating elective cesarean sections versus emergency cesareans and vaginal delivery. Therefore, HCV-infected women should not undergo elective cesarean section due to their HCV status, but there may be benefit in minimizing invasive procedures and the duration of rupture of membranes.

- **Breastfeeding**
  Breastfeeding has not been found to be associated with transmission of HCV from mother to infant.

**Follow-Up of Infants Born to HCV-Infected Women**
Most infants are HCV RNA negative at birth but become HCV RNA detectable by age 2 to 6 months if they have been infected. A proportion of infants who are initially HCV RNA positive will become HCV RNA negative with further follow-up. For this reason, it is recommended that testing of infants be delayed until age 12 to 18 months. Since HCV antibodies from the mother may remain detectable in the uninfected infant for more than 12 months, testing of infants for HCV antibody should not be performed until after age 18 months.

*Spontaneous clearance* of HCV infection among infants infected at birth occurs in up to 20% within the first 3 years of life. In the short term, these infants do not appear to have any serious complications of chronic infection but a subset of children may progress to cirrhosis over years.

**Risk of Cirrhosis and Liver Cancer in Women with HCV**
For the woman chronically infected with HCV, the serious risks of the disease are cirrhosis and liver cancer. These complications develop over several decades of infection and do not occur in all infected persons. Interestingly, most studies on the course of chronic HCV infection show a lower risk of cirrhosis liver cancer in women compared to men. Men have a two fold increased risk of their HCV infection progressing to cirrhosis than women. Data suggest that the reason women are “protected” from these complications is related to estrogen’s effect on liver diseases. The “high states” of estrogen are associated with decreased risk of scarring in the liver (fibrosis). Higher estrogen states during a woman’s life occur during pregnancy and with use of oral contraceptive or hormone replacement therapy.

Studies find that women that have had one or more pregnancies have less fibrosis in their liver than women who have never been pregnant. Women on birth control for an average of 5 years were found to have a lower score of fibrosis in their livers compared to women who did not use birth control. This association was not as strong as that found with pregnancy, but still follows the same pattern that higher states of estrogen maintained during a lifetime are associated with less liver damage.

The production of estrogen begins to decrease as women age and is at its lowest levels after menopause. The risk of progressive liver damage or fibrosis increases after women reach menopause. Replacement of estrogen through hormone replacement therapy in menopause has been associated with a decrease in the rate of progression and a lower risk of cirrhosis. Women that used hormone replacement therapy or estrogen therapy early in menopause were shown in studies to have a lower rate of fibrosis in their liver than women that did not participate in any hormone therapy.

HCV-infected individuals whose disease progresses to cirrhosis are at a higher risk for liver cancer or hepatocellular carcinoma. Liver cancer is more common in men than in women. However, the difference in risk between men and women decreases once women reach menopause. Menopause is associated with lower estrogen levels and the risk of liver cancer increases after a decline in estrogen occurs. This suggests that estrogen may be protective against the development of liver cancer.

There are several lines of evidence suggesting that estrogens may be important in reducing the risk of liver cancer in women with chronic HCV infection.
As with the risk of cirrhosis, studies show that women with a higher lifetime of estrogen were at less risk of developing liver cancer.\textsuperscript{18}

Higher lifetime estrogen levels are associated with multiple pregnancies and natural menopause occurrence, in comparison to early menopause mostly occurring due to surgical removal of uterus and ovaries.\textsuperscript{18}

Hormone replacement therapy also decreased a women’s risk of developing liver cancer.\textsuperscript{18}

Is Hormone Replacement Therapy (HRT) Advised in Women with HCV?

Menopause in the United States occurs, on average, at age 50. However, the body starts decreasing its production of estrogen and progesterone several years before menses stop. As discussed above, there are studies that show hormone therapy replacement is associated with a decrease in the progression of fibrosis as well as the risk of liver cancer.\textsuperscript{15,18}

However, this does not mean that all women with chronic HCV infection should use hormone replacement therapy (HRT). The decision to use HRT requires a careful weighing of potential risks and benefits of estrogen use.

Women with HCV infection can safely take HRT if this is desired. Studies have found no worsening of liver function or evidence of liver toxicity in women on HRT.\textsuperscript{19} Low doses combining estrogen and progesterone are safe to use.

Alcohol in Women with HCV

Alcohol can negatively affect the liver. Alcohol is processed by the liver and broken down into byproducts. These byproducts are toxic to the liver and accelerate liver damage. Regular alcohol usage can cause continuous damage to the liver, resulting in the development of progressive fibrosis and eventually cirrhosis. Drinking on average more than two alcohol beverages per day increases the risk of cirrhosis to a significant degree.\textsuperscript{20,21} Cirrhosis is approximately 20 times more likely to occur in individuals that drink greater than two drinks per day.\textsuperscript{20}

Studies show that women are more susceptible than men are to liver damage from alcohol.\textsuperscript{21-24} Women have a higher risk of developing alcohol-related liver damage and cirrhosis at any alcohol intake (see Figures 1 and 2).\textsuperscript{21}

![Figure 1. Relative risk estimated for the development of alcohol induced liver disease based upon sex and consumption of alcoholic beverages per week.](image-url)
Excess alcohol consumption can worsen the course and outcomes of HCV infected individuals. Data show that there is an increase in inflammation and fibrosis specifically in HCV-infected persons that consume more than 2 drinks per day. When specifically addressing women’s risk, data show that women drinking only one alcoholic beverage per day, still show an increase in inflammation and fibrosis. The reason that women are at a higher risk of liver damage from drinking the same levels of alcohol as men is unknown. These are some of the possible factors.

**FACTORS THAT MAY BE ASSOCIATED WITH INCREASED ALCOHOL DAMAGING EFFECT IN WOMEN**

- Women have a lower body mass and fluid content, which corresponds to higher alcohol concentrations in their blood in comparison to men who have ingested the same amount of alcohol.
- Women have decreased metabolism of alcohol in the stomach and delayed gastric emptying, which increases the amount of alcohol that is absorbed into the blood.
- Women have increased metabolism of alcohol in the liver. This may increase the concentration of alcohol byproducts that can damage the liver.
- Estrogen, present in higher amounts in women, increases the presence of factors that cause injury and inflammation in the liver with alcohol byproducts present.

Alcohol and hepatitis C are a dangerous combination, especially for women. Table 2 on the next page summarizes what is known about the effects of excess alcohol consumption on people living with HCV.
Table 2. Effects of Excess Alcohol Consumption in Persons Infected with HCV

<table>
<thead>
<tr>
<th>Effect</th>
<th>Description</th>
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<tbody>
<tr>
<td>HCV virus levels</td>
<td>May increase by an average of 0.8 logs when consuming &gt; 80g of alcohol a day.</td>
</tr>
<tr>
<td></td>
<td>There is significantly higher risk of progressing to cirrhosis in HCV patients who drink heavily when compared to those that do not drink.</td>
</tr>
<tr>
<td>Excess alcohol intake</td>
<td>Leads to a fatty liver and fat in the liver cells results in liver injury with inflammation and fibrosis.</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Increases the risk of liver cancer in HCV patients.</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>May reduce the effectiveness of HCV treatment. If the virus is cleared through treatment, alcohol usage may increases the risk of having a relapse or return of detectable virus after completing the treatment.</td>
</tr>
</tbody>
</table>

THE TAKE-HOME MESSAGE:

Abstinence is the safest means of ensuring that alcohol does not contribute to the negative effects of HCV infection. If alcohol is used, it is recommended that no more than 1 drink per day be consumed. 12 oz of beer, 5oz of wine or 1oz of liquor = 14g of alcohol.

Fat in the Liver: Effect on HCV

There is an increasing rate of obesity in the United States. One way to evaluate obesity on a standard scale, is to identify a person’s body mass index (BMI), which takes into account weight and height. The National Institutes of Health provides an online BMI calculator at www.nhlbisupport.com/bmi. Table 3 summarizes the interpretation of the BMI score.

<table>
<thead>
<tr>
<th>Interpretation of BMI</th>
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<tbody>
<tr>
<td>Under Weight</td>
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<tr>
<td>BMI &lt; 18.5</td>
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Facts About Obesity and Women

- Women have a higher likelihood of developing obesity over their lifetime than men, even if their body weight was healthy during adolescence and young adulthood.
- Almost 63% of women in the United States are overweight and 33% are obese.40, 41
- Women have a 60% risk for obesity by age 35.42 Obesity rates increase with age. Approximately 28% of adults aged 20 to 39 years were obese while 36.8% of adults aged 20 to 59 and 31% of those aged 60 years or older were obese.41
- As women age and progress through menopause their weight tends to increase, and there is high likelihood of being overweight or obese after menopause.43, 44

Being overweight or obese is associated with many health risks and diseases including liver disease. Excessive weight can cause a collection of fat to build up in the liver, a condition called steatosis. Steatosis can cause damage to the liver. Other conditions associated with the steatosis include type II diabetes, elevated levels of triglycerides, and certain
medications. Central or abdominal fat is associated with a higher rate of steatosis. There are two ways fat is carried, either centrally (abdominally) or more evenly spread over the body. The body type that accumulates fat centrally has been described as “apple” shaped. The more generalized distribution is described as “pear” shaped. Figure 3 shows the differences between more central fat storage (apple shaped) and more generalize a spread over the body (pear shaped).

Figure 3. “Apple” and “pear” body types showing differences in excess fat storage

Several studies in HCV-infected persons have shown an association between the presence of steatosis and a higher degree of liver inflammation and fibrosis. It has been suggested that accumulated fat within a cell causes its early death, and is associated with increased inflammation and ultimately with increased damage to the liver and fibrosis.

The cause of steatosis differs in individuals that are infected with different genotypes of HCV. There is a higher percentage of fat accumulation in the liver found with HCV genotype 3. There has been an association with high virus levels in genotype 3, which indicates that the virus itself may be contributing to the fat collection. In contrast, in individuals infected with HCV genotypes other than genotype 3, the fat in the liver is related to being overweight, having diabetes, or elevated triglycerides.

Obesity and steatosis in the liver can interfere with the effectiveness of hepatitis C treatment. With obesity, there is a greater body mass and this may reduce the amount of drug available in the body and impair the effectiveness of treatment. There is a decreased rate of sustained virus clearance in individuals with excess fat in their liver (determined through liver biopsies) compared to those without excess liver fat.

There is a higher risk for women to develop an unhealthy body weight with age, especially after menopause. Being overweight is a risk factor for worse disease outcome in HCV infection. Optimization of weight is an important issue.
for women infected with HCV. Data demonstrate that steatosis and inflammation in the liver can be reduced with even modest weight loss.\textsuperscript{55} Individuals with a BMI greater than 30 are urged to actively participate in weight loss regimens or programs. Being at a healthy weight is important to prevent many diseases and to improve quality of life. However, it is crucial in an HCV-infected individual, since being at an unhealthy weight can worsen liver disease, increase the risk of complications, and affect treatment success.

**HCV Treatment**

The current standard treatment for chronic hepatitis C infection is a combination of pegylated interferon and ribavirin. Pegylated interferon is an injectable medication taken once a week. Ribavirin is an oral medication that is taken twice daily. These medications work by trying to stop the virus from entering into the liver cells and from making copies of themselves. The length of treatment depends on the HCV genotype. Studies have determined the appropriate length of treatment for different genotypes and the success rates of eliminating HCV.

The most important determinant of likelihood of success of treatment is HCV genotype. The most common genotypes in the United States are 1, 2 and 3. For genotype 1, 48 weeks of treatment is recommended. This provides a 40\% to 50\% chance of eliminating the virus. Genotype 2 and 3 HCV are more sensitive to current treatment and require a shorter duration of treatment, 24 weeks. The success rate of eliminating the virus is 70\% to 80\%.\textsuperscript{56,57} Female sex has been associated with a higher likelihood of responding to HCV treatment in some but not all studies.\textsuperscript{57-60} In those studies reporting a difference, women have a 10\% to 20\% higher likelihood of achieving viral clearance with pegylated interferon and ribavirin compared to men.\textsuperscript{60}

There are several side effects associated with standard treatment and many patients report a temporary decline in their quality of life.\textsuperscript{61} Once through treatment, individuals that have a sustained viral response report an improvement in their quality of life.\textsuperscript{60,62} The most common side effects of treatment include fatigue, muscle aches, joint aches, itchy rash, nausea, insomnia, and depression. The medication can also cause a decrease in blood cell counts, both red blood cells (anemia) and white blood cells (neutropenia). There are several ways to manage these side effects while on treatment.\textsuperscript{64}

Certain side effects of the hepatitis C treatment affect women more frequently or severely than men.

- **Depression**
  Women are two times more likely to suffer from depression in the general population. HCV treatment is known to cause or worsen existing depression. It is more likely that women on treatment will have an issue with mood changes. Antidepressants are commonly used during HCV treatment to manage these symptoms.\textsuperscript{63}

- **Sexual issues**
  Overall dryness is a common side effect of treatment - dry skin, dry eyes, dry mouth. Specifically for women, vaginal dryness can cause issues with sex. This can be managed with lubricating gels.\textsuperscript{65}

- **Anemia**
  Women have a lower red blood cell count than men at the start of treatment and are therefore more likely to develop a decline in their blood counts that results in symptoms. Anemia can cause symptoms of fatigue, weakness, and shortness of breath. With the medication causing a decline in these counts, women can experience these symptoms earlier in treatment and more severely than men.

**Special Considerations Related to Pregnancy and Treatment**

HCV-infected women of childbearing age often seek guidance on the timing of antiviral therapy in the context of future pregnancy. The main reason for a woman to consider antiviral therapy prior to pregnancy is to eliminate the 5\% risk of HCV transmission to the infant. However, antiviral therapy prior to pregnancy results in delays in the time to conception, and treatment is successful in at best a variable proportion of those treated. Most importantly, treatment cannot be taken during pregnancy or when breastfeeding.
Ribavirin is teratogenic (causes birth defects in the fetus) and its use in women and in their partners trying to conceive and in those pregnant is absolutely contraindicated. The effects of ribavirin are prolonged and it is necessary to wait six months after the last dose of ribavirin before trying to conceive.

Summary

Risk Factors for Acquiring HCV
- An uninfected woman is more likely to acquire HCV through sex from an infected man than vice versa.
- Women who are in sexual partnerships with injection drug users are at risk for acquiring HCV in the partnership by engaging in risky injection and sexual practices.
- There is a low risk of transmitting or becoming infected with HCV in monogamous partnerships.

Pregnancy
- There is a 5% chance that HCV can be passed from a HCV-infected mother to her child.
- There is no treatment to interrupt or prevent the transmission of HCV at the time of birth.
- Current HCV treatments cannot be taken while trying to conceive or during pregnancy as they are extremely harmful to the fetus.

Hormone Replacement Therapy
- Hormone replacement therapy can be taken by women with HCV.
- There are studies that suggest that estrogen use may be protective against developing cirrhosis and liver cancer.

Alcohol Usage
- Women are more susceptible to alcohol’s effects on the liver and are at higher risk of developing cirrhosis than men drinking the same amounts of alcohol.
- It is recommended that women with HCV do not drink alcohol as it is not known if there is a safe level of alcohol intake. However, if a woman does drink, her intake should be a maximum of 1 drink per day.

Fatty Liver (Steatosis)
- Excess weight can lead to fat in the liver, which increases inflammation and liver damage. Fat in the liver is a risk factor for cirrhosis in HCV infected patients.
- Obesity and fat in the liver are associated with a decrease in the success rate of HCV treatment.

Hepatitis C Treatment
- Some studies suggest that women have a higher likelihood of achieving a sustained viral response to interferon-based therapy.
- Certain side effects of treatment (for example, depression and anemia) may occur more frequently or be more severe for women.
References


Chapter 18: Women and Hepatitis C
