Women with Chronic Hepatitis C Virus Infection: Recommendations for Clinical Practice

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Abstract: The natural history of hepatitis C virus infection differs between women and men. Women demonstrate a slow rate of disease progression until menopause. Older women are more likely to develop fibrosis and are less responsive than younger women to pegylated interferon and ribavirin. Women of childbearing age have higher rates of sustained virologic response, but current therapies are contraindicated during pregnancy. Vertical transmission of hepatitis C virus occurs, but data supporting recommendations for prevention of mother-to-infant transmission are limited.

Key Words: chronic hepatitis C, female sex, liver diseases

Approximately 3 million people in the United States are chronically infected with the hepatitis C virus (HCV),[1] which is transmitted primarily through contact with the blood of an infected person. Acute infection resolves in approximately 20% of cases and the rest develop chronic infection.[2] The major sequelae of chronic HCV infection are cirrhosis and hepatocellular carcinoma.[2] The clinical course varies widely among individuals, with sex influencing the natural history and clinical outcomes. Understanding the unique features in women will assist clinicians in managing female patients with chronic HCV infection.

Prevalence and Natural History of HCV in Women

Since the implementation of blood product screening, injection drug use (IDU) has become the most common mode of HCV acquisition.[1] Sex does not affect the risk of acquiring HCV. Although women in the United States historically have demonstrated a lower prevalence of HCV infection,[3] their sex likely reflected their lower rate of IDU[4] because sex differences in HCV prevalence are not seen in other cultures.[5] In addition, a meta-analysis of 30 studies reported that female prison inmates are 40% more likely than are male prison inmates to be infected with HCV.[6] Female injection drug users also exhibit higher rates of HCV infection than their male counterparts,[7,8] a difference that is related to behavior rather than biology: Female injection drug users frequently share injection equipment and engage in unsafe sex practices,[7,9] including having intercourse with people with whom they also inject drugs.[10,11]

Although sex does not appear to affect the risk of HCV infection, it does influence its outcome. A systematic review of 31 longitudinal studies found that 40% of women versus 19% of men will resolve acute HCV infection.[12] Genome-wide association studies have reported that genetic variation surrounding the interleukin-28B (IL-28B) locus is associated with

Key Points

- In the absence of comorbid conditions, women with hepatitis C virus (HCV) infection experience a slower progression to cirrhosis and a lower risk of hepatocellular carcinoma.
- Following menopause, the incidence of liver damage increases and women become less responsive to interferon-based therapies for chronic HCV infection.
- Abstinence from alcohol and maintenance of a healthy weight reduce the risk of liver disease progression in patients with chronic HCV.
- Achieving a sustained virologic response before conception may reduce substantially the risk of vertical HCV transmission; however, current therapies carry risks of fetal malformation.
- Fertile women who receive pegylated interferon and ribavirin should be counseled to use two forms of contraception. Because of drug–drug interactions with estrogen-based oral contraceptives, this form of birth control is unreliable in women receiving telaprevir or boceprevir.

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enhanced response to interferon-based therapies and spontaneous resolution of HCV infection.[13] A cohort study of Danish injection drug users noted that women with favorable IL-28B genotypes were six times as likely as women with unfavorable genotypes to spontaneously clear HCV infection[14]; however, even when controlling for the IL-28B genotype, women remain more likely than men to spontaneously clear HCV infection.[15]

Women also manifest slower progression to two major chronic HCV infection complications, cirrhosis and hepatocellular carcinoma. In a cohort of 376 Irish women chronically infected with HCV from contaminated anti-D immunoglobulin, only 1.9% had progressed to histological cirrhosis after a mean of 17 years following exposure.[16] The low rate of fibrosis progression was confirmed in a 25-year follow-up study of 167 women, of whom 1.2% developed histological cirrhosis.[17] Male sex was identified as an independent risk factor for developing hepatocellular carcinoma in several studies.[18,19] This sex-specific predilection for complications of liver disease is not completely understood. Some experts posit that higher estrogen states exert a protective effect on the liver.[20] Animal models suggest that estrogen suppresses hepatic fibrosis,[21–23] and a recent in vitro study proposed that estrogen inhibits the production of HCV virions.[24] Multiparous women exhibit lower stages of fibrosis than nulliparous women, and fibrosis progression accelerates after menopause.[25,26] In observational studies, women who received hormone therapy (HT) appeared to have a slower progression to fibrosis[20]; however, the benefits of HT in women with HCV have not been established. HT appears to be safe in women with liver disease when indicated for other reasons.[20]

Modifiable Risks for Progression of Liver Disease

Excessive alcohol intake accelerates the progression to HCV-related cirrhosis. Studies demonstrate consumption of >30 g/day increases the risk for cirrhosis in hepatitis C threefold.[27] Current guidelines stress the importance of abstinence from alcohol for all patients with HCV.[28] Accumulating evidence suggests that women infected with HCV are more vulnerable than their male counterparts to the effects of alcohol.[20] A prospective study illustrated that women who consumed >20 g/day doubled their risk for increased fibrosis, whereas men required >30 g/day to reach a similar risk increment.[29] Healthcare providers should encourage women with chronic HCV to abstain from alcohol or, alternatively, to limit intake to an equivalent of 12 g/day of ethanol.

Increased body mass index (BMI) also appears to accelerate disease progression, regardless of sex. Multiple studies have illustrated an increased risk for progression of liver disease in patients who are overweight (BMI $\geq$ 25 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2).[30–32] In a small prospective study of patients with chronic hepatitis C, a mean body weight reduction of 5.9 ($\pm$3) kg resulted in lower alanine aminotransferase levels and reduced levels of fibrosis on liver biopsy[33]; thus, even modest weight loss may reduce the risk of the progression of liver disease.

Effect of Sex and Age on Treatment Response

The primary goal of treatment of HCV is the prevention of cirrhosis and hepatocellular carcinoma by eradicating the virus. The surrogate marker for viral eradication is a sustained virologic response (SVR), defined as an undetectable serum HCV viral load 6 months after completing therapy. Studies of hepatic C therapeutics that examined SVR rates by sex reported conflicting findings. Overall, men and women appear to have equal responses to pegylated interferon and ribavirin.[34,35] When stratified by age, however, SVR rates for women dramatically decline with older age, a phenomenon that has not been observed in men[36–38] (Table 1). Similar to their protective effects on the progression of liver disease, higher estrogen states are hypothesized to promote SVR.[37] Studies of telaprevir or

Table 1. Studies that stratified sustained virologic response to interferon-based therapies by sex and age

	Women			Men		
Study	**Age group, y**	**SVR, %**	***P***	**Age group, y**	**SVR, %**	***P***
Hayashi et al[36]	<40	75	<0.0001	<40	33	<0.001
	≥40	16		≥40	25	
Sezaki et al[37]	<50	71	0.03	<50	69	0.41
	≥50	32		≥50	63	
Villa et al[38]	Premenopausal	68	<0.0001	<45	59	0.114
	Postmenopausal	46		≥55	50	

SVR, sustained virologic response.

Table 2. Summary of SVR rates by sex for phase III studies examining the addition of telaprevir or boceprevir to pegylated interferon and ribavirin

Study	Drug	SVR rate, women (%)	SVR rate, men (%)
Treatment naïve			
ILLUMINATE[39]	Telaprevir	77/89 (87)	169/197 (86)
SPRINT-2[40]	Boceprevir	181/284 (64)	294/450 (65)
Treatment experienced			
REALIZE[39,41]	Telaprevir	103/158 (65)	247/372 (66)
RESPOND-2[42]	Boceprevir	68/118 (60)	134/210 (63)

ILLUMINATE, Illustrating the Effects of Combination Therapy with Telaprevir; REALIZE, Retreatment of Patients with Telaprevir-based Regimen to Optimize Outcomes; RESPOND-2, Retreatment with HCV Serine Protease Inhibitor and PegIntron/Rebetol 2; SPRINT-2, Serine Protease Inhibitor Therapy-2; SVR, sustained virologic response.

boceprevir in combination with pegylated interferon and ribavirin illustrate equivalent response rates among men and women with genotype 1 HCV[39–42] (Table 2). These studies did not further stratify women by age, although in some studies older age was associated with overall lower rates of SVR.[35,43]

Pregnancy and Breast-feeding

Women with advanced liver disease are at increased risk for complications during pregnancy, but the effects of maternal HCV infection on natal outcomes are less well defined.[44] Recent evidence suggests that HCV infection may increase the risks for gestational diabetes, low birth weight, and neonatal intensive care unit admission.[45,46] Modifiable risk factors, such as IDU and limited prenatal care, may be more prevalent in patients with HCV,[41] which could confound data on maternal and fetal outcomes.

Pregnancy may improve the natural course of HCV infection. In the second and third trimesters, alanine aminotransferase levels decrease, whereas serum levels of HCV RNA increase.[47] This could imply that decreased hepatocyte damage, possibly related to increased estrogen levels and/or placental interferon production, occurs during pregnancy. Although alanine aminotransferase and HCV RNA serum concentrations return to prepregnancy levels within several months of delivery, women with multiple gestations do exhibit slower disease progression.[21]

Vertical transmission is the major cause of HCV infection in children.[45] Maternal–infant transmission occurs in roughly 5% of cases in which the mother is infected with HCV,[48] but recommendations regarding prevention are limited by insufficient high-quality data. The timing of transmission also is poorly understood; evidence exists for both in utero and transvaginal transmission.[49] Frequently identified risk factors for vertical transmission are high maternal HCV viral load and human immunodeficiency virus (HIV) co-infection.[50,51] Prolonged rupture of membranes (>6 hours) has been associated with more frequent perinatal transmission.[50] In addition, some experts recommend avoiding invasive procedures that promote fetal exposure to maternal blood, such as fetal scalp monitoring.[50,52] Elective cesarean section has been proposed to reduce the risk of vertical transmission[53]; however, this practice is not recommended for women infected with HCV unless they are co-infected with HIV.[52] Some studies have reported that because an elevated serum viral load increases the risk of transmission,[50,51] women who achieve remission from HCV before conception may reduce their risk of transmitting the virus to their fetuses.

Although HCV RNA has been detected in breast milk and colostrum,[54] breast-feeding does not appear to be a primary route of maternal–infant HCV transmission.[50,55] Some experts believe that the quantity of virions in these bodily fluids is insufficient to result in infection and that gastric acid exerts a protective effect.[52] Mothers infected with HCV are encouraged to breast-feed in the absence of other contraindications, such as HIV-1 co-infection, but they should be counseled that there is limited study on this topic.[56] The Centers for Disease Control and Prevention propose temporary interruption of breast-feeding when the mother has cracked, bleeding, or traumatized nipples, which could increase exposure of the infant to HCV.[57]

Antiviral Therapy in Women

Choosing when to initiate HCV therapy in women can be challenging, particularly with regard to maternal age and family planning. There is evidence that advanced age decreases the likelihood of an SVR in women more so than in men.[29,30] Given the risk of vertical transmission, it may be preferable to complete treatment in women of reproductive age before they conceive. Because use of ribavirin is contraindicated in pregnancy, women of childbearing age who are considering therapy for HCV require careful counseling regarding the potential danger to a child conceived during the treatment period.

Although ribavirin has not been studied formally in human gestation, several animal studies have demonstrated significant embryocidal and teratogenic effects; as a result, ribavirin is contraindicated during pregnancy (pregnancy category X).[58] The serum half-life of ribavirin is 12 days; the drug also is pooled in erythrocyte populations, which can result in prolonged post-administration exposure.[59] Two forms of effective contraception are required during and 6 months following therapy with ribavirin in women capable of conception.[58] Women who are capable of conception should be aware that if their male partners are receiving ribavirin, then the use of two forms of contraception during and 6 months after treatment is recommended. In addition, women of childbearing age should take a pregnancy test before treatment initiation and submit to monthly pregnancy tests during the treatment period.[58] Because ribavirin has not been studied in human pregnancy, women inadvertently exposed to ribavirin 6 months before or during pregnancy should consider enrollment in the Ribavirin Pregnancy Registry (www.ribavirinpregnancyregistry.com).

The effects of interferon on the fetus are uncertain (pregnancy category C). Interferon-α does not appear to cross the placental barrier or demonstrate teratogenic effects.[60] Case studies of pregnant women with leukemia have not demonstrated fetal malformation associated with interferon use, but intrauterine growth retardation has been observed in this setting.[61]

Boceprevir and telaprevir have been assigned to pregnancy category B by the Food and Drug Administration; however, these medications are administered exclusively with ribavirin and pegylated interferon-α, precluding any use during pregnancy. Both drugs are potent CYP3A4 substrates and inhibitors, resulting in many potentially dangerous interactions with other drugs, including oral contraceptives. Telaprevir and boceprevir may cause systemic hormonal contraceptives to be unreliable during concurrent administration.[62,63] Drosperinone concentrations double in the presence of boceprevir, contraindicating coadministration because of concern for potentiating hyperkalemia.[63] Barrier methods and intrauterine devices are the preferred methods of contraception in women receiving boceprevir or telaprevir in combination with pegylated interferon-α and ribavirin.[55,56] Given the wide range of drug–drug interactions involving these agents, close review of package inserts or consultation with a clinical pharmacist is recommended in patients receiving concomitant medications during therapy.[64]

Conclusions

The natural history of HCV infection differs between women and men. Women are more likely than men to clear acute HCV infection. With chronic HCV infection, women experience a slower progression to cirrhosis and are less likely than men to develop hepatocellular carcinoma. Accelerated disease progression occurs in postmenopausal women; older women also have lower rates than younger women of SVR to pegylated interferon and ribavirin. Infected women of childbearing age should be educated about the risks of perinatal HCV transmission and the potential teratogenicity of current treatment regimens. All women with HCV should be counseled on the effects of alcohol and obesity on the progression of liver disease.

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