SUPPLEMENT ARTICLE

Natural History and Management of Hepatitis C: Does Sex Play a Role?

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Hepatitis C virus infection is a disease that disproportionately affects men more than women. After initial HCV infection, women are more likely to clear the virus spontaneously. Women also have slower rates of liver disease progression than men if they become chronically infected. However, this rate of disease progression changes over time in women. Postmenopausal women have increased rates of fibrosis compared with women of reproductive age because they have lost the protective effects of estrogen. Estradiol and estrogen receptors in the liver protect hepatocytes from oxidative stress, inflammatory injury, and cell death, which all contribute to fibrosis. As a consequence of the overall slower liver disease progression and increased viral clearance in women, the disease burden from HCV infection is found predominantly in men. Although some studies have suggested higher sustained virologic response rates in HCV-infected women receiving dual therapy for HCV infection, this seems to be less important in the direct-acting antiviral era, when response rates for HCV therapy have increased so substantially that baseline demographic factors seem to have less of an effect on overall rates of cure.

Keywords. Hepatitis C; Sex; Gender; Women; Treatment.

More than 170 million individuals worldwide are infected with hepatitis C virus (HCV). Consequences of chronic infection include cirrhosis, end stage liver disease and hepatocellular carcinoma. In addition, HCV infection is the leading indication for liver transplantation in much of the developed world. It is most commonly spread through infectious blood but can also be acquired through sexual transmission. Risk factors for blood acquisition include birth to an HCV-infected mother, intravenous or intranasal drug use, receipt of contaminated blood products before screening for HCV, health care exposures before universal precautions, and other percutaneous exposures, such as unregulated tattoos and occupational needle-stick exposures.

Most individuals are asymptomatic with chronic infection until the late stages of disease, and risk-based screening has proved diagnostically ineffective for most persons with this disease. Therefore, current estimates probably grossly underestimate the burden of this disease. In the United States, it is projected that up to 85% of the estimated 3–5 million infected individuals are unaware of their condition [1]. In Europe, approximately 60%–90% of the 5–10 million chronically infected individuals remain undiagnosed [2]. New recommendations from the Centers for Disease Control and Prevention and the US Preventive Services Task Force for a one-time HCV antibody test for all individuals born from 1945 to 1965 will hopefully help identify most individuals living with HCV in the United States [1]. This "baby boomer" cohort, in particular, accounts for 75% of individuals living with HCV infection, and the disease has already demonstrated significant morbidity and mortality in this cohort [1, 3]. HCV infection disproportionately affects men more than women. In the United States, HCV antibody prevalence in men is nearly double that in women (2.1% vs 1.1% in women) [4]. In Europe, similarly, overall prevalence is also higher in men than women [5].

NATURAL HISTORY

Spontaneous Clearance of Infection

Studies have demonstrated that on average about 20% of individuals infected with HCV will spontaneously clear the virus after initial infection. Host factors such

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as *IL28b* genotype have been associated with spontaneous clearance [6]. Female sex has also been reported as an independent predictor of clearance in a cohort of individuals with acute HCV infection with various modes of transmission [7]. In a cohort of 632 patients with acute HCV infection, factors independently associated with time to spontaneous clearance included female sex (adjusted hazards ratio [AHR]: 2.16; 95% CI confidence interval [CI], 1.48–3.18), *IL28b* CC genotype (vs CT/TT; AHR, 2.26; 95% CI, 1.52–3.34), and HCV genotype 1 (vs nongenotype 1; AHR: 1.56; 95% CI, 1.06–2.30) [8]. The effect of the *IL28b* and HCV genotypes on spontaneous clearance was greater in female than in male patients. High rates of spontaneous clearance have also been described in 2 cohorts of women infected peripartum in 1977 with anti-D immunoglobulin contaminated with HCV genotype 1b, one in Ireland (46%) and the other in Germany (44%) [9, 10]. Large population analyses also support this higher rate of clearance in women. Based on the National Health and Nutrition Examination Survey (NHANES) data from 1999 through 2002 in the United States, chronic infection will develop in about 89% of men and 63.4% of women [4]. One study in Egypt in a cohort of >4000 adults with predominantly genotype 4 HCV infection found the overall clearance rate to be 38.5%. Independent of age and modes of acquisition, infection cleared spontaneously in more women than men in this analysis (44.6% vs 33.7%; $P = .001$) [11].

Disease Progression

Many host factors affect disease progression, including modes of transmission, age at time of infection, duration of infection, human immunodeficiency virus (HIV) coinfection, steatosis, and insulin resistance. Sex is also among the factors that predict disease progression. Cross-sectional studies aimed at examining fibrosis in individuals living with hepatitis C have identified male sex as an independent risk factor for disease progression. Poynard et al [12] analyzed 3 large cohorts in France and identified an overall 39% increase in the annual rate of fibrosis progression in men compared with women (0.154 in men vs 0.111 in women; $P < .001$), correlating with differences in the median duration of progression to cirrhosis (26 vs 36 years, respectively) .

Most studies to date examining the natural history of HCV infection in female cohorts have relied on long-term follow-up of women infected with HCV through contaminated anti-D immunoglobulin. Admittedly, these cohorts represent a relatively homogenous population of young women, but they do consistently demonstrate a low rate of disease progression. In a group of Irish women infected in 1977 with genotype 1b, only 2% had progressed to definitive cirrhosis after 17 years of follow-up [9]. A similar cohort of women infected peripartum with contaminated immunoglobulin in Germany has also been followed longitudinally [10]; 25 years after infection, cirrhosis had developed in only 0.5% of these women. A recent update 35 years after infection still showed a low but increased rate of disease progression, with signs of cirrhosis in 9.3% of patients [13].

The analysis of this German cohort suggests that the risk for disease progression in women changes over time. This change in disease progression has been linked to reproductive status in women with HCV infection. A retrospective analysis of a large cohort of women stratified by reproductive status found that disease progression was slow in women of reproductive age and increased significantly after menopause. Age-matched men had more severe fibrosis than women of reproductive age, in premenopause, and in early menopause. No significant difference in fibrosis was seen between women in late menopause and the age-matched men in the cohort [14].

Effects of Estrogen

It is postulated that this difference in disease progression is linked to the protective effects of estrogen on the liver. Estradiol and estrogen receptors in the liver protect hepatocytes from oxidative stress, inflammatory injury, and cell death, which can all contribute to fibrosis. Estrogen also probably plays a suppressive role in hepatocarcinogenesis [15]. Although the exact mechanism is not fully understood, in vivo and in vitro data also suggest that estradiol inhibits activation of hepatic stellate cells, which play a central role in hepatic fibrosis [16]. Additional data from animal models show that when both female and male rats are treated with dimethylnitrosamine (DMN) to induce fibrosis, female rats have less evidence of fibrotic change. Moreover, when the ovaries of the female rats are removed or the male rats are pretreated with anti-estradiol antibody, the level of fibrosis increases with DMN treatment. In both male rats and female rats after ovariectomy, estradiol replacement then decreases the amount of fibrosis induced by DMN [17].

The effect of estrogens on women with chronic HCV infection was examined in a large retrospective cohort analysis. The study showed that history of pregnancy and an exposure to hormone replacement therapy were both associated with decreased fibrosis progression. Women with a history of oral contraceptives had lower mean fibrosis scores, although oral contraceptives had no statistically significant effect on the rate of fibrosis progression [18]. Changes in fibrosis progression for women may also be altered by other risk factors that change with age. For instance, in the German cohort of women followed up after infection with contaminated anti-D immunoglobulin, cirrhosis was associated with higher body mass index. Interestingly, 20 years after infection only 10% of this cohort had an abnormal body mass index (>25 kg/m^2) compared with 63% of women 35 years after infection, suggesting that this risk factor for disease progression may also change over time [13].

Effects of Alcohol

Many studies suggest that alcohol consumption accelerates liver fibrosis for individuals living with HCV infection. In their

retrospective analysis of the impact of alcohol on liver histology and clinical progression, Wiley et al [19] demonstrated that persons who are infected with HCV and drink alcohol have a higher rate of cirrhosis and progress faster to decompensated liver disease. Findings of other studies suggest that the amount of alcohol may be important in assessing this risk [12]. Some sex distinctions influence the effects of alcohol on individuals with HCV infection. First, study findings suggest that men are more likely to engage in heavy drinking than women [20]. Even so, the threshold at which alcohol may negatively affect disease progression seems lower in women than in men. In a prospective analysis, Hezode and colleagues [21] analyzed the relationship between reported alcohol consumption—stratified as minimal (1–20 g/d), mild (21–30 g/d), or moderate (31–50 g/d)—and liver histologic features. Not surprisingly, the proportion of patients with significant fibrosis (F2–F4) grew with increased alcohol intake. They found that the percentage of women with F2–F4 fibrosis was 31% for those with an alcohol intake of <20 g/d and 60% for those with an intake of >20 g/d ($P = .02$). A similar trend was seen in men, but with a higher threshold of alcohol consumption. For men, the proportion with F2–F4 disease was 32.2% at <30 g/d and increased to 65.5% at >30 g/d ($P = .004$) [21].

Disease Burden and Sex

With women having a slower rate of disease progression, it is not surprising that the burden of HCV disease complications mainly affects men. Using a mathematical model, Davis et al [22] predict that the number of cases of cirrhosis in the United States is only increasing and expected to peak in 2020 at 1.04 million cases. They estimate that 73.6% of cirrhosis cases occur in men and that cases in men will continue to make up the majority during the next 20 years (Figure 1). During the peak incidence years in the 1970s and 1980s, the incidence of acute HCV infections was similar in women and men (43% vs 50.3%); however, as of 2009, a smaller proportion of women have developed cirrhosis because of increased clearance and decreased rates of progression. Davis et al [22] report a similar trend with projected cases of hepatocellular carcinoma and decompensation from liver disease.

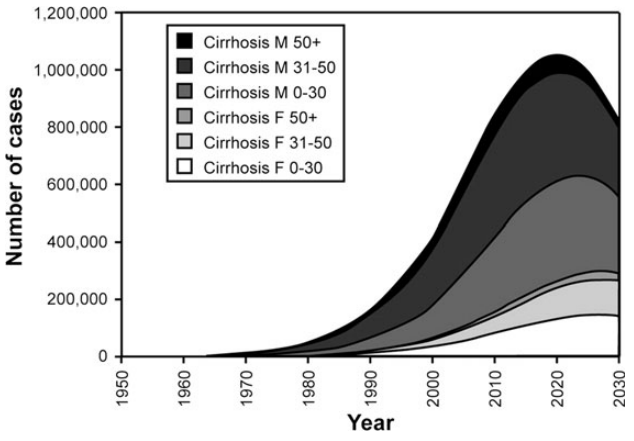

Figure 1. Stacked prevalence curves showing number of cirrhosis cases by year according to sex and age at initial hepatitis C virus infection (reprinted with permission from Davis et al [22]).

PREGNANCY AND MOTHER-TO-CHILD TRANSMISSION

Pregnancy does not adversely affect the progression of hepatitis C, and women with HCV infection do not have a higher rate of pregnancy or birth complications compared with uninfected women [23]. Although universal prenatal screening of women for HCV is not currently recommended, vertical transmission is the most common cause of HCV infection in children. Studies vary widely with regard to reported rates of transmission, but on average the reported rate of transmission is 5% [24]. The risk of transmission is directly related to the level of HCV RNA in the mother [25]. Mode of delivery, labor management, and breastfeeding practices have been investigated to assess risk of transmission of HCV to the infant. Some studies have linked vaginal deliveries and intrapartum fetal monitoring to HCV acquisition. However, a recent systemic review by the US Preventative Services Task Force for Mother-to-Infant Transmission of HCV concluded that there was no clear evidence that caesarian delivery provides benefit over vaginal delivery [26]. In addition, breastfeeding posed no significant risk of transmission to the infants. There were data suggesting risk with prolonged rupture of membranes and some conflicting evidence regarding internal fetal monitoring [26]. Currently, the World Health Organization supports breastfeeding for HCV-positive mothers, except when the nipples may be cracked or bleeding. It does not recommend a special method of delivery but does caution against invasive fetal monitoring.

RISK OF SEXUAL TRANSMISSION

Most studies show that only a small percentage of persons acquire HCV through unprotected heterosexual intercourse. In a recent study of monogamous heterosexual couples, Terrault et al demonstrated that the maximum incidence rate of HCV transmission by sex was 0.07% per year (95% CI, .01–.13) or approximately 1/190 000 sexual contacts [27]. For this reason, persons in long-term, monogamous relationships need not change their current sexual practices, although they should discuss safer sex practices if either partner is concerned about transmission. Those individuals who have multiple sex partners have a higher risk of contracting HCV infection. Men who have sex with men are at increased risk for sexual transmission of HCV. Risk factors associated with transmission of HCV in men who have sex with men are HIV coinfection, multiple partners, sexual

practices associated with mucosal trauma, and recreational drug use [28]. For individuals with multiple sexual partners, the recommendation is to use barrier protection with latex condoms. Some studies indicate that sexual transmission from men to women is more efficient than transmission from women to men, as is also the case with HIV [29]. Because HCV is spread through blood, it is more likely to be sexually transmitted when a woman is having her menstrual period.

RESPONSE TO HCV THERAPY

Sustained virologic response (SVR) to HCV therapy has been linked to decreased rates of HCV-associated morbidity and mortality [30]. HCV therapy is in an era of rapid change. The mainstay of therapy is expected to shift from pegylated interferon α and ribavirin to all oral therapy with direct-acting antivirals with or without ribavirin in the next few years. Most of the current data available on HCV treatment is from outcomes with pegylated interferon and ribavirin and with triple therapy for genotype 1 with the addition of a protease inhibitor (either telaprevir or boceprevir). Findings of some studies on treatment of HCV with pegylated interferon and ribavirin suggest that women may have an increased SVR with this therapy [31]. Others have not shown much difference in outcomes in men compared with women [32].

Earlier studies looking at differences in response rates in standard interferon therapy found age to be predictive of SVR in women. There was no difference overall between the sexes, but being a younger female patient (aged <40 years) did favor better treatment outcomes [33]. It has been postulated that the varied reports of the effect of sex on SVR might be related to reproductive status, with varying response rates for women before and after menopause. High treatment response rates have been reported with pegylated interferon and ribavirin in young women [34]. Villa et al [35] examined the effect of reproductive status for women on SVR, and they found that menopause, not age, independently predicted a lower rate of SVR for women.

Raloxifene, an oral selective estrogen receptor modulator prescribed for postmenopausal women to prevent the progression of osteoporosis, has been examined as adjunctive therapy for the treatment of HCV infection in this population. In a small group of patients with genotype 1b disease studied in Japan (n = 123), the addition of raloxifene to pegylated interferon and ribavirin improved SVR rates from 34.4% to 61.3% compared with pegylated interferon and ribavirin alone ($P = .005$) [36].

The dramatically improved cure rates with direct-acting antivirals make the effect of sex potentially much less relevant, but it remains an interesting question. Data from the treatment-naive trials for telaprevir and boceprevir showed no significant different in the sexes in treatment outcomes [37, 38]. Phase 3 data with sofosbuvir support a trend for better treatment responses in women (Univariate analysis in the NEUTRINO study in Genotypes 1, 4, 5, and 6 with odds ratio (OR) of 2.154 [$P = .084$] and the FISSION study in Genotypes 2 and 3 with an OR 2.349 [$P = .006$]), but more data is needed [39]. Clearly, the balanced inclusion of HCV-infected women into HCV trials remains crucial to our ability to answer these questions.

SPECIAL CONSIDERATIONS IN HCV THERAPY

Current treatment for HCV infection, as well as some of the newer regimens, includes the use of ribavirin. Ribavirin is a known teratogen with major implications for fetal abnormalities if administered during pregnancy. Current recommendations for both women and female partners of men starting HCV therapy are that they use 2 forms of contraception during and for 6 months after ribavirin therapy to avoid any adverse consequences (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021511s023lbl.pdf). For women undergoing HCV therapy, some of the direct-acting antivirals, such as the protease inhibitors given as part of combination therapy, pose significant drug-drug interactions with oral contraceptives. Therefore, women taking protease inhibitors as part of combination therapy for HCV infection cannot rely on hormonal therapy as a method of contraception. Intrauterine devices in combination with a barrier method of contraception are one potential approach for these women while they are receiving HCV therapy. Incidentally, this drug-drug interaction can also lower the levels of hormone replacement therapy for postmenopausal women. Clinical monitoring is currently recommended when these agents are given in combination.

In conclusion, HCV infection affects men and women differently. Women are more likely to have spontaneous clearance of the virus and less likely to have disease progression if they are chronically infected. However, this risk for fibrosis in women changes over time and is directly related to reproductive status. As women age, they are at increased risk of complications from this infection. As we move into an era of more-potent and better-tolerated therapy, the disparities in treatment outcomes are likely to lessen. However in both men and women, the burden of the disease will continue to be lasting and significant in the years to come.

Note

Potential conflicts of interest. R. B. serves on an advisory board for Gilead Sciences, has an educational grant from Vertex Pharmaceuticals, and is an author for Up to Date. J. K. R. has received honoraria for speaking at educational events or consulting from Abbvie, Abbott, Bionor, Boehringer, Bristol-Myers Squibb, Gilead, Janssen, Merck, Novartis, Tobira, Vertex, and ViiV and is an author for Up to Date. M. B. has received honoraria for speaking at educational events or consulting from Abbvie, Boehringer, Bristol-Myers Squibb, Gilead, Janssen, Merck, and Novartis.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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