Gender specific medicine in liver diseases: A point of view

Marilena Durazzo, Paola Belci, Alessandro Collo, Vanessa Prandi, Erika Pistone, Maria Martorana, Roberto Gambino, Simona Bo

Abstract
Gender medicine focuses on the patho-physiological, clinical, prevention and treatment differences in diseases that are equally represented in men and women. The purpose of gender medicine is to ensure that each individual man and woman receives the best treatment possible based on scientific evidence. The concept of “gender” includes not only the sexual characteristics of individuals but also physiological and psychological attributes of men and women, including risk factors, protective/aggravating effects of sexual hormones and variances linked to genetics and corporal structures that explain biological and physiological differences between men and women. It is very important to consider all the biological, physiological, functional, psychological, social and cultural characteristics to provide patients with individualized disease management. Herein, we critically analyze the literature regarding gender differences for diseases and acquired conditions of the most representative hepatic pathologies: primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, non alcoholic fatty liver disease and alcoholic liver disease, and viral chronic hepatitis B and C. The last section addresses hemochromatosis, which is a prevalent iron overload disorder in the Caucasian population. This review aims to describe data from the literature concerning viral chronic hepatitis during pregnancy, management during pregnancy and delivery, and new effective drugs for the prevention of maternal infection transmission without significant adverse effects or complications.

Key words: Gender; Liver disease; Primary biliary cirrhosis; Autoimmune hepatitis; Viral chronic hepatitis B; Viral chronic hepatitis C; Non alcoholic fatty liver disease; Alcoholic liver disease

Core tip: Gender medicine focuses on the patho-physiological, clinical, prevention and treatment differences in diseases that are equally represented in men and women. The concept of “gender” includes not only the sexual characteristics of individuals but also physiological and psychological attributes of men and women. In this review, we critically analyze the literature regarding gender differences for diseases and acquired conditions of the most representative hepatic pathologies: primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, non alcoholic fatty liver disease and alcoholic liver disease, viral chronic hepatitis B and C, and hemochromatosis (the prevalent iron overload disorder in the Caucasian population).

INTRODUCTION

Gender medicine is a new aspect of medicine that focuses on investigating the differences in diseases based on anatomic and physiological stages, from biological, functional, psychological, social and cultural points of view and analyzes the range of responses to pharmacological care. This field emerged because epidemiological and clinical surveys performed over the last 30 years have generally reported results for only gender [1].

The concept of “gender” refers not only to the sexual characteristics of individuals, but also to a set of differences derived from the physiology and psychology of men and women and from various social and cultural environments. From biological and physiological points of view, the differences between men and women may be explained by differences in the presence of risk factors, protective/aggravating effects of sexual hormones, variances linked to genetics and various corporal structures [2].

The aim of this review is to examine the available data in the literature concerning the differences between men and women for the most representative hepatic pathologies, including primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH), viral chronic hepatitis B and C, non alcoholic fatty liver disease (NAFLD) and alcoholic liver disease. There are morphological differences in the liver between genders. Thus, hepatic damage may produce different consequences in men and women in ongoing primitive diseases and during acquired conditions [3].

AUTOIMMUNE LIVER DISEASES: PRIMARY BILIARY CIRRHOSIS, AUTOIMMUNE HEPATITIS AND PRIMARY SCLEROSING CHOLANGITIS

Previous studies have examined gender differences in the immune system, and suggest that estrogen and androgen may modulate the immune system. Women have a significantly higher number of CD4+ T lymphocytes and a higher CD4+/CD8+ ratio than men [4].

Additionally, the secretion of interferon-γ (IFN-γ) and interleukin (IL)-10 was enhanced after the addition of estrogen in T-cell clones isolated from women [5]. Conversely, androgen inhibited, the secretions of IFN-γ, IL-4, and IL-5 in murine T cells [6].

These findings suggest that gender differences could have a role in autoimmune diseases.

The best example demonstrating gender differences is PBC.

PBC is a chronic cholestatic liver disease characterized by immune-mediated inflammatory destruction of the small intrahepatic bile ducts, and fibrosis. PBC can progress to cirrhosis and subsequent liver failure [7-9]. PBC is a typical female disease that occurs from 40-60 years of age [10]. The incidence rates in women and men range from 3:1 to 22:1, with an average incidence rate in women of 10:1 [10]. The age at PBC diagnosis was found to be older in men (62 years) than in women (51 years) [11].

Numerous hypotheses have been formulated to justify this sex imbalance. For example, the effects of sex hormones in lymphocyte maturation/activation and the synthesis of antibodies and cytokines have been suggested as contributing factors. Additionally, the immune-modulatory effects of estrogens during reproductive life, fetal microchimerism, skewing of the X-chromosome inactivation pattern and defects in sex chromosomes have also been suggested as factors [12]. Several studies have identified an increased incidence of X haploinsufficiency in female patients [13-14].

A study by Selmi et al [15] indicates that epigenetic factors, such as X chromosome inactivation, may also be involved in the development of PBC, and variable concordance rates of PBC have been identified between twins. A recent study by Lleo et al [16] demonstrated how Y chromosome loss is associated with PBC in male patients. These epigenetic changes may be ideal targets for new personalized treatments, as suggested by cancer data. However, no convincing evidence has yet supported any of these hypotheses. Males are less likely to be symptomatic than females. Females experience pruritus as a single symptom more often than males. It has been suggested that female sex hormones may be linked with pruritus. In addition, female sex hormones may cause more abdominal pain/discomfort and constitutional symptoms (malaise, anorexia, weight loss, fatigue). In contrast, males experience more jaundice, jaundice with pruritus, and upper gastrointestinal bleeding [17].

The rates of severe daytime somnolence and depressive symptoms were found to be similar in males and females; in contrast, autonomic symptoms were more profound in females [18,19].

Concomitant autoimmune diseases such as, Sicca Syndrome, Scleroderma and Raynaud’s phenomenon, were shown to be less prevalent in men. These findings suggest that females are more likely to suffer concomitant autoimmune disease than males. The complications of hepatocellular carcinoma (HCC) in patients with PBC were reported to be significantly greater in men than in women [20]. Biochemical levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (gGT) were reported to be slightly higher in symptomatic males compared to asymptomatic males, but both were higher than in females [21]. The only histological difference identified were that symptomatic female patients had more piecemeal necrosis of the liver and that symptomatic males had more stainable copper storage than asymptomatic males. Additionally, symptomatic females were reported to have more pseudoxanthomatous transformation than asymptomatic females [22].

AIH is a liver disease characterized by progressive inflammatory destruction of the parenchyma. AIH is associated with the presence of circulating autoantibodies, hypergammaglobulinemia and interface hepatitis on liver biopsy. AIH typically responds to immunosuppressive therapy [23].
Primary biliary cirrhosis  Autoimmune hepatitis

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<tr>
<th>M/F ratio 1:3</th>
<th>M/F ratio 1:3.6</th>
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<tr>
<td>Age at diagnosis higher in M than in F (62 yr vs 51 yr)</td>
<td>Normalization of ALT levels after 6 mo of corticosteroid treatment less frequent in M than in F</td>
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<td>M less symptomatic than F: pruritus, abdominal pain/discomfort and constitutional symptoms more common in F; jaundice and upper gastrointestinal bleeding more common in M</td>
<td>Better long-term survival and outcome in M than F</td>
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<td>Concomitant autoimmune diseases more common in F (sicca syndrome, scleroderma, Raynaud phenomenon), whereas HCC complication are significantly greater in M</td>
<td>Decrease of severity during second trimester of pregnancy and possible onset of acute exacerbation after delivery</td>
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<td>ALP, ALT and gGT higher in M than F</td>
<td>Haplotype HLA A1-B8-DR3 more prevalent in M than in F</td>
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<td>Piecemeal necrosis and pseudoxanthomatous transformation greater in symptomatic F</td>
<td>Higher frequency of concurrent immunological disorders at presentation in F than M</td>
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HCC: Hepatocellular carcinoma; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; gGT: Gamma-glutamyl transpeptidase; HLA: Human leukocyte antigen; F: Female; M: Male.

The etiology of AIH is unknown, though both genetic and environmental factors are involved. It has been suggested that the major mechanism of liver damage is the failure of impaired regulatory T cells to control immune reactions against liver host antigens.

The actual prevalence of AIH is unknown. AIH is characterized by a strong female preponderance (the female/male ratio is 3.6/1). There are no sex or gender differences in age, form of clinical onset, frequency of symptomatic concurrent autoimmune diseases, and human leukocyte antigen DR (HLA DR) status. Various studies have demonstrated that in men, there is a minor frequency of normalization of ALT stages after 6 mo of corticosteroid treatment. However, men with AIH appeared to have better long-term survival and outcome than women. In females the severity of AIH was found to be likely to decrease during the second trimester of pregnancy, when estrogen was secreted at high levels and acute AIH exacerbation occurred after delivery. High levels of estrogen are associated with an anti-inflammatory milieu. Moreover females have a higher frequency of concurrent immunological disorders such as Sjogren Syndrome at presentation than males.

Al-Chalabi et al discovered the extended haplotype HLA A1-B8-DR3 (associated with increased susceptibility to AIH) was more than twice as prevalent in male patients as in female patients with AIH.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts. PSC leads to cholestasis, progressive hepatic fibrosis and eventually decompensated cirrhosis.

The incidence of PSC is 1:100000 people. Previous studies have demonstrated that PSC is more prevalent in men than in women (M > F 7:3). In the United States, between 62% and 70% of patients are male. The pathogenesis of PSC is unclear because it is a complex immune-mediated disease. The most accepted theory is that in genetically predisposed individuals, the environmental exposure to infective agents or toxins causes persistent immunemediated damage to cholangiocytes and progressive destruction of bile ducts, which leads to chronic cholestasis (Table 1).

**ALCOHOLIC LIVER DISEASE**

Alcohol abuse and its various complications are still widespread in the Western world and represent a frequent cause of hepatic damage. The excessive consumption of alcohol may cause hepatic steatosis, alcoholic hepatitis and cirrhosis. Alcoholic cirrhosis causes approximately 40% of deaths due to cirrhosis. The severe forms (hepatitis, cirrhosis) are associated with ingestion of 160 g/die of alcohol in 10-20 years. The incidence of alcoholic liver disease increases proportionally with the consumption of alcohol. Several surveys have demonstrated that hepatic damage develops faster in women than in men. In cases of heavy drinkers with a weekly consumption of 336-492 g, the relative risk of developing cirrhosis was equivalent to 7 in men and 17 in women. Furthermore, the relative risk of developing alcoholic liver disease was 3.7 in men and 7.3 in women. The factors regulating in the differences in susceptibility to alcoholic toxicity include the following: age during alcohol consumption, the manner of alcohol consumption (with or without meals) and the nutritional state of the individual.

Women are more susceptible to damage by alcohol compared to men, which leads to more advanced liver disease after alcohol consumption. It has been demonstrated that, under the same conditions and assuming equal doses of alcohol, women reach higher blood ethanol concentrations than men. Moreover, it has been shown that females have a major risk of hepatitis progression toward cirrhosis after abstaining from alcohol. The causes attributed to these gender differences include differences in corporal structures, different enzymatic activity and hormonal differences.

The process of metabolizing a substance before it enter the general circulation is called first-pass metabolism. Various studies have demonstrated that an isofrom of gastric alcohol dehydrogenase (ADH) has a main role in alcohol metabolism. ADH activity is linked to the first passage of alcoholic metabolism and affects the blood ethanol concentration. At the gastric level, this enzyme is expressed less in women than in men. Furthermore, in a female heavy drinker the activity of gastric ADH is practically absent. Therefore in women a majority of alcohol reaches the liver directly, which may worsen the hepatic damages. Moreover, this situation contributes to the gen-
NAFLD

NAFLD is the most common chronic liver disease in the Western world, affecting 30% of the general adult population\[38\].

NAFLD is an umbrella term for a group of diseases defined by a hepatic fat infiltration in > 5% of hepatocytes, in the absence of excessive alcohol intake. Excessive alcohol intake is defined as two standard drinks (20 g ethanol) daily for men and one standard drink (10 g ethanol) daily for women. NAFLD encompasses a histological spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH). NASH is defined by steatosis, hepatocellular damage and lobular inflammation\[39\] in individuals without significant alcohol consumption and without viral, congenital and autoimmune liver disease markers.

There have been parallel increases in the prevalence rates of obesity, metabolic syndrome (hyperglycemia, visceral obesity, hyperlipidemia and hypertension) and NASH. As a result, NASH is considered part of metabolic syndrome (MS)\[40\].

MS is a risk factor for cardiovascular disease, its high prevalence has substantially affected public health in recent years\[41\]. There are varied reports in the literature regarding the gender distribution of MS. Several studies report a higher incidence of MS in men than in women, but the reverse has been shown in other reports\[42\].

The prevalence of MS increases with the general population age and is more likely in black and Hispanic female populations. The accumulation of hepatic and intrahepatic fat is not different between genders, but it is affected by dietary lipid consumption\[43\]. Abdominal fat tissue is a major source of free fatty acids and cytokines for the liver, and fat favors the early development of insulin resistance, dyslipidemia, and high blood pressure. The more favorable fat distribution in women demonstrates why women need a higher degree of adiposity to achieve the same metabolic disturbances as men\[44\]. Subcutaneous and visceral adipose tissue types are influenced by age and gender. Visceral adipose tissue accumulates more rapidly with age and weight gain in males and postmenopausal females than in younger females\[45\]. The difference in the prevalence of MS between genders has been attributed to sex hormones. Many studies have shown that, in postmenopausal women, the distribution of their body fat changes toward visceral adiposity\[46\]. There are differing reports in the literature concerning the association between gender and NASH. In some studies, NAFLD was approximately 1.5 times more prevalent in females than in males whereas other studies did not find any differences, between genders\[47,48\]. Some studies have shown that female gender is a risk factor for NASH\[49\], but the current literature presents conflicting results\[50,51\]. A population, based study suggested that endogenous estrogens have a protective role in NASH, which may explain why the prevalence of NAFLD increases in women over 50 years of age\[52\].

In conclusion, although the sex differences for fibrosis in patients with NAFLD are not identical, women tend develop more, severe fibrosis than men\[53\].

The possible roles of estrogen in hepatic lipid metabolism and fibrosis require further investigation (Table 3).

CHRONIC HEPATITIS B

Protracted treatment with nucleoside/nucleotide analogs has allowed for an improvement in the natural history of patients with chronic hepatitis B virus (HBV) infection by reducing the incidence of cirrhosis and the risk of complications\[54\].

Over the last 20 years, the epidemiology of HBV infection has radically changed in Italy. At the beginning of the 1980, the rate of HBV surface antigen (HBsAg) carriers in the general population was 3.5%, with peaks of 10% in Southern Italy. The current prevalence of carriers is less than 1%, and a majority of carriers are male. The rate of chronic infection is higher in men due to various factors and is widely studied. However, it is unclear if men are exposed to more viruses, or if men have a less effective immune response in eliminating. The major re-
HBV and pregnancy

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<td>perinatal transmission (telbivudine)</td>
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Table 4  Chronic hepatitis B during the pregnancy and in the foetus

HBV: Hepatitis B virus; F: Female; FDA: Food and drug administration.

response in females is caused by the position of genes that determine the response, and most genes are located on the X chromosome. This hypothesis is supported by the female prevalence of two hepatic autoimmune diseases (PBC and AIH).[59]

HBV does not meaningfully influence fertility, and contracting an HBV infection during a pregnancy does not increase morbidity or maternal or fetal mortality.[60] Recent evidences demonstrated that the increased production of proinflammatory cytokines in chronic hepatitis B (CHB)[61,62] may participate in the development of complications, such as gestational diabetes, pre-delivery hemorrhages and pre-term delivery.[63] Furthermore, in women with cirrhosis, there are higher frequencies of gestational hypertension, detachment of the placenta and pre-partum hemorrhages compared with healthy controls.[64]

A normal pregnancy with elevated levels of corticosteroid hormones and estrogens cause increased HBV viremia[65] and indices of cytolysis (ALT)[66]. Moreover, there have been reported cases of peripartum hepatitis with hepatic decompensation.[67]

The main cause of fetal HBV transmission is delivery. The administration of immunoglobulins and an anti-HBV vaccine may prevent fetal infection in more than 85% of children born from HBsAg+ mothers.[68]

Other minor causes of fetal and maternal transmission are intrauterine transmission (HBV may reach the foetus through the placental barrier)[69] and transmission during breastfeeding through virus ingestion or by contact with maternal cutaneous lesions.[70]

There is currently no clear therapeutic way to prevent viral transmission. The pre-delivery administration of immunoglobulins has yielded discordant results[67,68]. The study by Beasley demonstrated that the administration of immunoglobulins and anti-HBV vaccine within 12 h of birth reduced the frequency of HBV transmission from > 90% to 26%.[69,70]

A 2012 Chinese study evaluated the safety of lamivudine treatment for CHB in early pregnancy. This study examined 92 chronic HBV-infected pregnant women who received Lamivudine treatment either before pregnancy or in early pregnancy. These women were not co-infected with hepatitis C virus (HCV), human immunodeficiency virus, cytomegalovirus, or other viruses. Adverse events were observed throughout the entire pregnancy and perinatal period. The effectiveness of Lamivudine treatment for blocking mother-to-infant transmission of HBV was evaluated. The data showed that treatment does not increase complications or adverse events for mothers during pregnancy or the perinatal period. Additionally, no effect on fertilization or embryonic development was found, and treatment did not increase the incidence of congenital abnormalities in infants. Furthermore, treatment reduced the rate of mother-to-infant transmission.[71]. A case report described a treatment with triple therapy of Lamivudine, IFN-beta and prednisolone for acute CHB exacerbation during pregnancy. The patient’s liver enzymes became elevated toward the end of the first trimester. She was treated with Lamivudine, interferon-beta and steroids early in the second trimester. After this treatment, aminotransferase levels rapidly normalized within 4 wk. Lamivudine was continued until delivery. Spontaneous delivery occurred at 37 wk of gestation. There were no congenital anomalies, and fetal growth was found to be within normal reference ranges. This case report suggests that combination therapy with Lamivudine, IFN-beta and steroids may be safely used during the pregnancy to treat acute CHB exacerbations.[72].

There are ongoing studies investigating the use of antiviral medicines in mothers with high HBV DNA levels. Currently the oral antivirals Telbivudine and Tenofovir are classified as “FDA pregnancy category B”, whereas the other antiviral drugs are classified as “FDA pregnancy category C”. A recent meta-analysis has demonstrated that Telbivudine use in the final stage of pregnancy is effective in preventing or reducing the perinatal transmission of HBV without meaningful or unfavorable effects.[73]

Some data exist on tenofovir in HIV positive women but these data show increased congenital malformations, kidney damage and distorted bone metabolism after exposure in utero.[74] (Table 4).

CHRONIC HEPATITIS C

HCV infection affects 130-170 million people worldwide, which is approximately 2%-3% of the global population. HCV is transmitted by parenteral routes, such as contact with infected blood or contaminated materials and intravenous drug injection with contaminated syringes. Although less common, HCV can be transmitted by sexual contact with HCV-positive partners[75,76]. Several studies have demonstrated that women have less altered hepatic biochemical tests and lower rates of fibrosis progression.[77]. These findings are related to the protective effects of estrogens, which possess anti-fibrotic properties. Estrogens have a role in blocking fibrogenesis in hepatic
stage of pregnancy (Pregnancy FDA Category X) (Table 5).

**GENETIC HEMOCHROMATOSIS**

Iron is essential for many biological processes. The liver stores iron and plays a central role in the regulation of iron metabolism. The liver synthesizes hepcidin, which is the most important iron regulatory hormone.

Genetic hemochromatosis (GH) is a prevalent iron overload disorder in the Caucasian population. Patients absorb more than the normal amount of iron through the intestine. Hepcidin is suggested to play a role in GH.

GH is not a gender-specific disease, but more males than females present symptoms and signs of hemochromatosis. Men accumulate more iron and have a higher incidence of liver injury.

The clinical symptoms of GH usually begin later in women than in men, likely due to the physiological loss of blood in women of childbearing age. The gender-specific regulation of hepcidin synthesis in the liver may play a role in this process.

The prevalence of the disease in men may also be explained by the greater extrahepatic deposition of iron in males than in females. In addition, serum ferritin levels are higher in men, which suggests that men have increased extrahepatic iron stores.

In conclusion, the clinical presentation of GH is different between women and men. Both liver disease and diabetes are more common in men, whereas fatigue and pigmentation are more common in women.  

**CONCLUSION**

Gender medicine focuses the scientific community on understanding and analyzing clinical, patho-physiological, prevention and treatment differences in diseases that are equally represented in men and women.

Current medicine offers better care through the study of disease mechanisms based on gender differences by focusing on the incidence and etiology of pathologies, clinical objectives and the response to therapies. The purpose of this field is to provide the best treatment possible to each individual man and woman based on scientific evidences.

This review emphasized the importance of appropriate management of viral chronic hepatitis during pregnancy and summarized the strategies to prevent mother-to-child transmission. The review focused on maternal and perinatal outcomes, disease progression and its impact on pregnancy, and the new effective drugs used to treat chronic HCV infection. Several studies have demonstrated that the sustained virological response (SVR) rate is significantly higher in women than in men, and fertile women with normal genotypes have a 100% chance of obtaining a SVR. Therefore the administration of combined therapy is not recommended during pregnancy (Pregnancy FDA Category X) (Table 5).
Very active treatment options be considered in the future.

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