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Female gender in the setting of liver transplantation

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Abstract

The evolution of liver diseases to end-stage liver disease or to acute hepatic failure, the evaluation process for liver transplantation, the organ allocation decision-making, as well as the post-transplant outcomes are different between female and male genders. Women's access to liver transplantation is hampered by the use of model for end-stage liver disease (MELD) score, in which creatinine values exert a systematic bias against women due to their lower values even in the presence of variable degrees of renal dysfunction. Furthermore, even when correcting MELD score for gender-appropriate creatinine

determination, a quantifiable uneven access to transplant prevails, demonstrating that other factors are also involved. While some of the differences can be explained from the epidemiological point of view, hormonal status plays an important role. Moreover, the pre-menopausal and post-menopausal stages imply profound differences in a woman's physiology, including not only the passage from the fertile age to the non-fertile stage, but also the loss of estrogens and their potentially protective role in delaying liver fibrosis progression, amongst others. With menopause, the tendency to gain weight may contribute to the development of or worsening of pre-existing metabolic syndrome. As an increasing number of patients are transplanted for non-alcoholic steatohepatitis, and as the average age at transplant increases, clinicians must be prepared for the management of this particular condition, especially in post-menopausal women, who are at particular risk of developing metabolic complications after menopause.

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Key words: Liver transplantation; Female gender; Estrogens; Model for end-stage liver disease score; Creatinine; Gender donor-recipient match

Core tip: Gender differences play an important role in liver diseases, their evolution and outcome, and in liver transplantation, not only in terms of access to this resource, but also in terms of graft survival, metabolic aspects, and quality of life after liver transplantation. Not only gender differences, are important, however, but clearly the different hormonal status throughout a woman's lifetime determines many aspects not only regarding fertility and sexual issues such as pregnancy, but also metabolic complications. Notwithstanding this, decision-making algorithms regarding indications, risk factors, and outcomes after transplant do not yet incorporate many of these concepts that affect the clinical practice.

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INTRODUCTION

It is ever clearer that gender differences play an important role in liver diseases, their evolution and outcome, and in liver transplantation (LT), not only in terms of access to this resource, but also in terms of graft survival, metabolic aspects, and quality of life after LT. Nevertheless, proposed measures for correcting the systematic bias disadvantaging women's access to LT, and the gender variable itself, are not yet fully incorporated into decision-making algorithms regarding evaluation of indications, risk factors, and outcomes in LT. The present review, therefore aims at highlighting gender differences in diseases that lead to LT, access to LT, and outcomes after transplant.

GENDER DISPARITY IN ACCESS TO LT

Sociodemographic determinants

Access to a life-saving resource such as LT has unfortunately been hampered for ethnic minorities, women, and patients of low socioeconomic status or inadequate insurance coverage; in a study analyzing health care inequities that prevent patients with end-stage liver disease from being evaluated and waitlisted for LT, patients were less likely to undergo evaluation, waitlisting and transplantation if they were women, black and lacked commercial insurance ($P < 0.001$ each)^[1].

This disparity of access to LT probably owes to several factors, including body and organ size considerations, differences in the etiology of the underlying liver disease, and limits of the model for end-stage liver disease (MELD) score, especially regarding creatinine levels^[2].

MELD, MELD-related issues and non-MELD determinants of access to LT

In the pre-MELD era, a study from the Organ Procurement and Transplantation Network (OPTN) showed that female sex was significantly correlated with longer stay on the liver transplant waiting list and also with the risk of dying before LT^[3]. Unequal access to LT for women was unfortunately perpetuated upon implementation of the MELD score for organ allocation, however. In a study based on UNOS data comparing pre- and post-MELD cohorts, women were more likely than men to die or become too sick for LT post-MELD [23.7% *vs* 21.4%; odds ratio (OR) = 1.30; $P = 0.003$] *vs* pre-MELD (22.4% *vs* 21.9%; OR = 1.08; $P = 0.37$). Similarly, women were less likely than men to receive a liver transplant within 3 years both pre-MELD (64.8% *vs* 67.6%; OR = 0.80; $P = 0.002$) and post-MELD (39.9% *vs* 48.7%; OR = 0.70; $P < 0.001$)^[4]. Actually, organ allocation based on MELD score has further increased gender disparity, as waiting list mortality risk has risen, particularly for MELD

scores > 15 ^[5]. In fact, female gender, together with primary non-function, fulminant hepatic failure, blood group O, CTP ≥ 11 and MELD score ≥ 20 have been found to be predictors of waiting list mortality^[6].

A systematic bias against women, resulting in part from the use of creatinine as a measure of renal function, has been identified in MELD-based liver allocation. Women's lesser body (and muscular) mass determines lower creatinine levels, one of the most important determinants of MELD score; due to the employment of creatinine instead of weight-adjusted glomerular filtration rate (GFR), the degree of renal dysfunction is likely in women is likely underestimated. Thus, MELD scores will be lower in women than in men with the same degree of renal compromise, which inevitably leads to a decreased access for women to LT^[2]. Moreover, attempts at correcting creatinine-induced MELD bias against women by including estimated GFR have not improved discrimination for 3-mo mortality after enrolment for LT^[7]. Likewise, the accuracy of MELD score in predicting 3- and 6-mo mortality in female LT candidates did not improve with the employment of the Modification of Diet in Renal Disease formula^[8]. Providing that renal function assessment was adequately corrected for gender, a negative bias against women would still remain, since women are more likely than men to suffer from autoimmune liver diseases, including primary biliary cirrhosis, which are less likely than hepatitis C (HCV) to lead to kidney dysfunction and higher MELD scores^[2].

Moreover, aside from the inaccuracy of MELD score in terms of renal dysfunction assessment in female patients, it is well known that patients with certain pathological conditions are poorly served by this score, including refractory ascites, refractory encephalopathy, recurrent cholangitis, and intractable pruritus in cholestatic diseases^[9], the latter of which encompass mainly women^[10-12]. Nevertheless, some of these conditions constitute symptom-based MELD exceptions and are awarded extra MELD points^[13].

On the other hand, standard exclusions to MELD, which are more regularly applied, include the presence of hepatocellular carcinoma (HCC)^[14-18], which is more common in men, further increasing the disparity of access to LT. After the implementation of the Milan Criteria^[14], the number of LTs for HCC has increased worldwide and currently in Europe about 27% of all LT patients have HCC with countries peaking over 40%^[19]. While exception points have greatly improved access to transplantation for HCC patients^[20], recent studies suggest that the current point scheme inadvertently prioritizes HCC over patients without HCC diagnosis (non-HCC) by overestimating the presumed risk of tumor progression^[21,22]. Even more vexing is the observation that even for equal MELD scores, women are at a disadvantage with respect to men in terms of LT access, suggesting that other factors must play a role in the gender disparity documented for LT rates^[7,23].

GENDER DIFFERENCES IN INDICATIONS FOR LT

According to the OPTN records for LT performed in the US

between January 1, 1988 until December 31, 2013^[24], a search for gender by diagnosis outlines several significant gender differences: significantly more women than men underwent LT for Wilson disease (410/47608 *vs* 326/78534, $P < 0.0001$), primary biliary cirrhosis (4796/47608 *vs* 809/78534, $P < 0.0001$), drug-induced acute hepatic necrosis (748/47608 *vs* 295/78534, $P < 0.0001$), Budd Chiari syndrome 441/47608 *vs* 233/78534), autoimmune cirrhosis 3025/47608 *vs* 959/78534, $P < 0.0001$), cryptogenic cirrhosis (4245/47608 *vs* 5009/78534, $P < 0.0001$), and non-alcoholic steatohepatitis (NASH) (1673/47608 *vs* 1875/78534, $P < 0.0001$).

On the contrary, significantly more men underwent LT for alcoholic cirrhosis (11195/78534 *vs* 3227/47608, $P < 0.0001$), alcoholic cirrhosis with HCV (4938/78534 *vs* 888/47608, $P < 0.0001$), HCC (2768/78534 *vs* 899/47608, $P < 0.0001$), HCC and cirrhosis (77555/78534 *vs* 2099/47608, $P < 0.0001$), HBsAg + Hepatitis B (2778/78534 *vs* 651/47608, $P < 0.0001$), and HCV (18187/78534 *vs* 8135/47608, $P < 0.0001$)^[24].

Viral hepatitis

Several studies have demonstrated a differential effect of gender on the outcomes of patients infected with HCV, showing that in female patients, the natural history of HCV virus infection tends to be characterized by slower rates of progression to advanced liver disease, with better response rates to antiviral therapy^[25-28]. Moreover, overall lower death rates for HCV-related liver disease as well as lower rates of HCC are observed in female patients^[29].

Regarding menopausal course of HCV-related liver disease, however, recent studies have reported that the reduced estrogen levels that characterize this state may determine the accelerated progression to fibrosis and higher rates of no response to antiviral therapy observed in this subpopulation, especially in genotype 1 HCV-infected patients^[30-32]; a statistically significant increase of tumor necrosis factor- α and interleukin-6 occur in menopause, and these proinflammatory cytokines have been associated to increased resistance to interferon-based therapy^[33]. A higher SVR rate with Peg-IFN α -2b plus ribavirin *vs* IFN α -2a plus ribavirin has been documented in menopausal women, which likely corresponds the former's pharmacokinetic properties that allow the drug to reach visceral fat and oppose the increased cytokine production and enhanced inflammatory status in menopause^[34].

Regarding hepatitis B (HBV), although significantly more men than women are transplanted for chronic HBV, LT for fulminant HBV is significantly more frequent in women^[35]. As well, hepatitis E virus (HEV) is unfortunately associated with disproportionately high rates of fulminant hepatitis in pregnant women, particularly during the third trimester, with case-fatality rates in epidemics ranging from 0.2%-4% in the general population, *vs* 10%-25% in the pregnant population^[36-38], possibly reflecting hormonal changes that increase susceptibility to a more aggressive course^[39].

Non-alcoholic steatohepatitis

NASH has increased in frequency as indication for LT^[40-42], and is bound to become one of the principal

indications in many Western countries, with the increasing worldwide prevalence of this entity^[43], and with the advent of new-acting direct antiviral agents, which will probably contribute to decreasing the percentage of HCV patients who necessitate LT.

In a study analyzing characteristics of patients referred for LT evaluation due to NASH ($n = 71$) from 1998 to 2008, and compared to the non-NASH possible candidates ($n = 472$)^[44], it was found that patients with NASH were older (58.7 years *vs* 52.5 years, $P < 0.0001$) and more likely of female gender (50.7% *vs* 32.1%, $P = 0.003$). As expected, NASH patients were more likely to suffer from diabetes, hypertension, obesity, and cardiac disease ($P < 0.05$). Moreover, for paired MELD scores, NASH was associated with similar bilirubin levels (2.34 mg/dL *vs* 3.16 mg/dL; $P = 0.11$), but significantly increased creatinine values (1.26 mg/dL *vs* 0.98 mg/dL; $P = 0.0018$) and lower international normalized ratio (INR) values (1.14 *vs* 1.27; $P = 0.04$), in contrast with LT candidates without NASH, respectively. This suggests that NASH is associated with renal dysfunction, which is translated into greater priority, as established by the MELD calculus.

Thus, MELD score in this setting might not truly reflect liver dysfunction, but could be more directly related to features of the metabolic syndrome, including microvascular renal damage associated with diabetes and hypertension. Therefore, the disadvantage posed to women by creatinine's weight in the MELD calculus formula might be outweighed in the future, with increasing number of patients being transplanted for NASH, most of them being of female gender. However, the present state of the matter is yet far from this scenario, as only 5%-8% of LT are currently performed for this indication, and the time needed for MELD's disparity to be counterbalanced by this theoretical female gender benefit is expectedly long^[2].

Putting together all these data is especially concerning, since women are generally more likely to have GFR < 60 mL/min per 1.73 m² previous to LT with respect to men, and the presence of this factor (OR = 3.28, $P \leq 0.001$), aside from female gender (OR = 2.96, $P < 0.001$) and age (OR = 1.09, $P < 0.001$), has been demonstrated to be independently predictive of stage ≥ 3 chronic kidney disease (CKD) at 1 year post-LT^[45]. In addition, this same study demonstrated that female gender (OR = 2.52, $P = 0.004$), age (OR = 1.05, $P = 0.003$) and NASH (OR = 2.95, $P = 0.039$) were independently predictive of \geq stage 3 CKD at 5 years post-LT.

Considering, that NASH LT recipients are more frequently women, that women's renal dysfunction is not adequately accounted for by creatinine measurement and thus not well served by MELD score, together with the fact that women are more likely to have compromised renal function prior to transplant, and that this variable predicts advanced CKD after LT, it becomes clear that this population stands a particular risk and should be addressed more carefully.

Autoimmune hepatitis

Differences in sex-hormone (estrogen and androgen) modulation of the immune system may be responsible

for gender variations observed in autoimmune disorders; women have a significantly higher number of CD4+T lymphocytes and a higher CD4+/CD8+ ratio than men^[46], secretion of interferon- γ (IFN- γ) and interleukin 10 (IL-10) are enhanced after the addition of estrogen in T-cell clones isolated from women^[47], while androgens have been demonstrated to inhibit the secretion of IFN- γ , IL-4, and IL-5 in murine T cells^[48].

Autoimmune hepatitis, characterized by progressive inflammatory destruction of the liver parenchyma associated with the presence of circulating autoantibodies, hypergammaglobulinemia and interface hepatitis on liver biopsy, is strongly preponderant in females (female/male ratio is 3.6/1)^[49]. Although corticosteroid treatment tends to achieve transaminase normalization more frequently in female patients^[50], women appear to have worse long-term survival than men^[51].

Primary biliary cirrhosis

Primary biliary cirrhosis, a chronic cholestatic liver disease characterized by immune-mediated inflammatory destruction of the small intrahepatic bile ducts and fibrosis, affects predominantly women with respect to men, with incidence rates ranging from 3:1 to 22:1, with an average incidence rate in women of 10:1^[52]. Gender differences also characterize the evolution of the disease: diagnosis of PBC is usually established at a younger age in women (51 years in women *vs* 62 years in men)^[53]. Women are more likely to be symptomatic, and experience pruritus as a single symptom more often than males, while jaundice, jaundice with pruritus, and upper gastrointestinal bleeding are more frequently manifested in men^[54]. Some symptoms such as severe daytime somnolence and depressive symptoms seem to affect men and women in an equal proportion, while autonomic symptoms seem to be more severe in women^[55,56]. The presence of concomitant autoimmune disorders such as Sicca syndrome, overlap syndrome, and autoimmune hepatitis, also determining a more aggressive course and generally poorer response to therapy, is more frequent in women, especially in those of Hispanic origin, as has been recently demonstrated in a US cross-sectional study^[57]. Development of hepatocellular carcinoma, however, seems to be more frequent in men^[58]. Although PBC entails a high risk of postmenopausal osteoporosis, it seems to be more associated with the severity of chronic liver disease, rather than specifically the PBC etiology^[59], and a recent Cochrane database systematic review reported that in female patients with cirrhosis, hormone replacement had no effect on all-cause mortality, fractures, liver-related mortality, liver transplantation, liver-related morbidity, serum bilirubin concentration nor lumbar spine bone mineral density. On the contrary, hormone replacement significantly increased the frequency of adverse events^[60].

Wilson disease

Although this autosomic recessive disorder characterized by a wide spectrum of clinical manifestations should theoretically be present in females and males in equal

proportion^[61], a slight female predominance has been reported^[62] partly reflecting the variable penetrance of genetic mutations that cause this disease. More significantly, however, neurological symptoms have been more frequently associated with female gender ($P = 0.051$) and with an acute, often fulminant course upon presentation when there is hepatic involvement ($P = 0.046$)^[63]. In a French study analyzing medical records of 121 patients who underwent LT for Wilson Disease, male gender, pre-transplant renal insufficiency, non-elective procedure, and neurological indication for LT were significantly associated with poorer survival rate ($P = 0.04$) at univariate analysis. However, none of these factors remained statistically significant on multivariate analysis^[64].

Alcohol

Alcohol has been demonstrated to exert a more deleterious effect in women and female animal models with respect to males^[65], which can partly be explained by lower levels of gastric alcohol dehydrogenase in females, resulting in lower alcohol threshold for women^[66]. Moreover, acute liver injury develops more rapidly and more extensively in women than in men even for a smaller quantity consumed^[67]. Ethanol has been demonstrated to increase TNF- α mRNA expression and cause more severe acute liver injury in females^[68]. Interestingly, estrogens have a major influence on Kupffer cell reactivity and proinflammatory cytokine production, and this could constitute a major determinant of women's increased risk of alcohol-induced liver disease^[69].

Drug-induced liver injury and gender

Different patterns of drug-induced liver damage between males and females have been recognized both in humans^[70] as well as in animal models^[71]. It has been reported that overall, women have a 1.5- to 1.7-fold greater risk of developing adverse drug reactions than men^[72], and a prospective, multicenter study based on intensive pharmacovigilance confirmed a higher risk of acute adverse drug reactions in women *vs* men^[73]. Excluding behavioural or dosing differences, there are three main hypotheses regarding the mechanisms behind these differences, including: (1) different pharmacokinetics between females and males; (2) gender-specific hormonal effects or interaction with signalling molecules that may affect drug safety; and (3) differences in aberrant immune response that targets the liver following drug exposure that can result in adverse drug reactions^[70]. Gender-based differences that may have an impact on drug pharmacokinetics and subsequent toxicity include differences in gastrointestinal blood flow, gastric acid secretion, relative amount of circulating drug-binding proteins, relative proportions of muscular and adipose tissue, renal blood flow, gender-specific expression of cytochrome P450 (CYP450) isozymes, as well as physiologic and hormonal changes during the menstrual cycle, during pregnancy and after menopause^[74].

A study based on World Health Organization-endorsed VigiBase™, the largest and most comprehensive database

on global “Individual Case Safety Reports”, analyzed gender and age differences in reporting of drug-induced hepatic failure for a 10-year period (2000-2009). From a total of 6370 reports from 38 countries, and excluding missing gender data in 379 cases, females accounted for 54.03% of cases. The largest proportion of hepatic failure cases corresponded to patients younger than 55 years (42.57%), with a female predominance (56.81%), whereas gender was almost evenly distributed in the group above 55 years of age. Regarding drug types, there was a significant female preponderance in hepatic failure associated with analgesics, antiepileptics, anti-inflammatory and antirheumatic agents, antidiabetics, and antibacterials for systemic use, whereas males were significantly overrepresented in hepatic failure cases associated with antivirals^[75].

Female gender is more frequently associated with paracetamol overdose, which fortunately only in a fraction of patients leads to acute liver injury and acute liver failure; in a study from Iceland analyzing 1913 drug-related poisoning episodes, of which 352 involved paracetamol overdoses, the female/male ratio was 3.0, and the principal age group was 16-25 years. However, amongst those who required hospitalization, 16% were accidental overdoses and there were no gender differences^[76].

HCC

In spite of the striking preponderance of male sex amongst patients with HCC, probably estrogens play a very important role in liver carcinogenesis^[77] and wild-type vs variant estrogen receptors in the liver accurately predict survival in patients with HCC^[78]. If transplant centers maintain the adopted trend of allocating nearly 17%-40% of organs to patients who have HCC^[19,79], women, whom are listed for LT less frequently for this indication, will have a reduced access to LT with respect to men, since while men will have theoretically 100% of organs available, women will have to “compete” against men for the remaining organs allocated to non-HCC indications for LT.

Notwithstanding the fact that HCC affects men more frequently, and that previous database studies had found gender disparities favouring men in rates of LT in cohorts of HCC patients only, a recent retrospective US database analysis spanning 10 years and over 40000 patients^[80] demonstrated that women with HCC present less often with decompensated liver disease (OR = 0.79, $P < 0.001$), and are more likely to receive invasive HCC treatment, with significantly higher rates of resection across different ethnicities and diagnoses (OR = 1.34 and 1.44, $P < 0.001$). In this study, univariate analysis showed that although women have lower unadjusted rates of LT, disparity resolves after controlling for other clinical and demographic factors^[80].

ISSUES OF SIZE AND GENDER IN DONOR-RECIPIENT MATCHING

Liver donor size mismatch has been proposed as partially accountable for the disparity between LT rates between

male and female patients^[2]. A large study based on the OPTN demonstrated that, controlling for region and blood type, women were 25% less likely to undergo LT in a given month in comparison with men ($P < 0.001$). Including gender within the model increased the OR for this variable to 0.84. Of this 25%, 9% was found to be attributable to MELD score. Stemming from this study, an additional 3% increase in the OR for gender (0.87, $P < 0.001$) is imputable to estimated liver volume (mean estimated liver volume was significantly lower for female patients than for male patients on the LT waiting list, $P < 0.001$), therefore partly explaining gender disparity in LT rates^[81]. Henceforth, even after accounting for MELD score and estimated liver size, approximately half of the 25% gender disparity remains unexplained.

In fact, other relevant factors related to survival on the waiting list for LT, such as the metabolic and nutritional status, are not accounted for by the MELD score. Notwithstanding the fact that in general women are characterized by less muscle mass than men, this difference is furthermore often not evaluated nor compensated for with adequate formulas^[82]. The standardized triceps skinfold thickness and mid-arm muscular circumference determinations, which are more adequate for evaluation of nutritional status than body mass index in patients with ascites, were found to be lower in female patients^[83]. Moreover, in a recent study analyzing pretransplant muscle mass on more than 300 LT recipients, of whom 68% could have been defined as cachectic, in female patients, muscle mass predicted intensive care unit stay, total length of stay, and days of intubation, but did not predict survival after LT (mean follow-up of 2.8 years)^[84].

The impact of gender mismatch between donors and recipients on the outcome of LT is still a matter of debate, and may differ amongst deceased-donor LT (DDLT), living-donor LT (LDLT), and pediatric LDLT. Lehner *et al.*^[85] reported that gender mismatch does not play a role in the outcome of LT. On the contrary, some studies have reported on the negative impact of gender mismatch on graft failure, specifically regarding male recipients who receive grafts from female donors in DDLT^[86-89]. Furthermore, a recently published prospective study analyzing outcomes of 1042 LT recipients demonstrated that graft survival in patients who received an organ matched for their gender was better than those receiving a gender mismatch ($P = 0.047$), and the worst combination was female-to-male LT ($P < 0.001$)^[90].

Regarding LDLT, a male recipient receiving a graft from a female donor was shown to be an independent risk factor for recipient mortality in adults^[91], while in pediatric LDLT, an interesting finding has been that recipients of maternal grafts have reportedly lower rates of graft failure and refractory rejection in contrast with recipients of paternal grafts^[92]. In the specific setting of HCV infection, no difference has been observed in terms of graft nor patient survival according to donor-recipient gender matching^[93].

Being smaller, female patients have a limited access to the pool of available organs, and may have to wait longer for organs of an appropriate size, since livers from

pediatric donors are preferentially allocated to children awaiting LT. Further increasing this disparity is the fact that a small organ may be adequate for a large individual, but the contrary is not always possible^[2].

Interestingly, a Japanese study analyzing 114 LDLT using parental grafts performed for recipients with biliary atresia demonstrated that gender mismatch alone was an independent risk factor for acute cellular rejection ($P = 0.012$), and paternal grafts with gender mismatch were associated with a higher incidence of acute cellular rejection with respect to maternal grafts with gender match ($P = 0.002$)^[94]. The authors infer that maternal antigens may have an important clinical impact on graft tolerance in LDLT, which is in line with what was first hypothesized by Starzl *et al.*^[95] regarding induction of tolerance by microchimerism, and what has been demonstrated regarding non-inherited maternal antigens and maternal microchimerism in blood and various organs^[96,97]. Exposure to maternal antigens, in fact, may have tolerogenic effects on offspring, resulting in acceptance or rejection of allografts expressing the maternal antigens^[98], although a functional linkage between microchimerism and tolerance has been difficult to establish^[99,100].

Another factor that might play a relevant role in gender-matching is the different hormonal array regarding estrogens (and their receptors). Female-to-female matched LT have been associated with a decreased risk of graft failure with respect to male-male matched transplants, but only for non-HCV female recipients^[86]. In animal models, a greater degree of hepatic lactic acidosis during warm ischemia has been demonstrated to occur in females with respect to males^[101], which may provide a potential metabolic explanation for the worse outcome in recipients of female donors. However, the matter entails complex aspects that have not yet been fully understood, and this is reflected by the disparity in reports on the role of estrogens in ischemia-reperfusion^[102-105]. Apparently, females are more susceptible to hepatic reperfusion injury, but experimental data in the mouse model have shown that estrogens actually reduce ischemia/reperfusion damage^[106]. The mechanisms for sex differences in the liver's metabolic response to ischemia do seem, however, to be estrogen-mediated, even in the presence of male hormones^[107].

However, again, not all of these differences may be attributable to hormone status solely, but may actually represent an immunological basis. Late-presenting nonanastomotic biliary strictures after LT have been reported to occur more frequently in female-male gender donor-recipient matches, as well as in patients transplanted for primary sclerosing cholangitis, and in patients in whom Roux-en-Y bile duct reconstructions were performed^[108], and while ischemia and preservation factors seem to play a preponderant role in early-presenting non-anastomotic biliary strictures, immunological factors are the predominant factor in late-presenting non-anastomotic biliary structures. Interestingly, the fact that immunological processes are implied, does not rule out the fact that still poorly understood linkages between hormones, hormonal receptor, and immunological mechanisms exist.

OUTCOMES AFTER LIVER TRANSPLANTATION IN FEMALE RECIPIENTS

Overall outcomes after LT, especially in the long-term, are reportedly better in women^[24] with respect to men. A 20-year follow-up study of 313 LT recipients revealed that, together with primary indication ($P < 0.001$), age ($P < 0.001$), impaired renal function at 6 mo ($P < 0.001$) and retransplantation ($P = 0.034$), gender ($P = 0.017$) had a significant impact on patient survival^[109]. The reported protective effect of female gender in the development of metabolic complications related to hyperglycemia^[109] has been confirmed in other series as well; a study based on the OPTN/United Network Sharing (UNOS) database including 19582 DDLT non-diabetic recipients (in whom the incidence of new-onset diabetes after transplantation (NODAT) has been established to be greater with respect to LDLT recipients), demonstrated that male sex was a predictor for NODAT, while this was not the case for LDLT recipients^[110].

After LT, de novo NASH or non-alcoholic fatty liver disease (NAFLD) reportedly develop in 20% and 10% of cases, respectively^[92], while approximately 50% of patients transplanted for NASH will experience recurrence^[90], with 5% to 10% of patients progressing to cirrhosis^[91]. Importantly, menopausal status, which is associated with weight gain and increased central fat mass^[111], constitutes a risk factor for developing NASH and metabolic syndrome; in a long-term observational study spanning 12 years, metabolic syndrome was a significant risk factor for mortality in postmenopausal women compared to men and premenopausal women^[93].

Regarding renal function, as mentioned above, in a recent study, female gender was found to be an independent and significant predictor of advanced stages of CKD at 1 year post-LT (OR = 2.96, $P < 0.001$) and at 5 years post-LT (OR = 2.52, $P = 0.004$)^[45], and results from the MOST study had revealed that 1-year GFR is significantly affected both by HCV infection and recipient female gender ($P < 0.01$ for both)^[112].

The impact of gender on outcomes after LT varies according to the indication for LT. Along with recurrent HCC ($P < 0.001$) and retransplantation ($P = 0.01$), female gender ($P = 0.002$) has been significantly associated with worse survival after LT for Hepatitis B, as shown in a multicenter US study pooling 738 LT recipients^[113]. Concerning HCV, post-LT recurrence is nearly universal^[114-116], and female gender has been described as a risk factor for severe HCV recurrence and graft lost after LT, and the risk increases with increasing donor age^[86,117,118]. The important fibrosis suppression effect of estrogens demonstrated experimentally in animal models^[119,120] is reflected in the clinically slower fibrosis progression observed in women with respect to men in chronic HCV^[121,122]. However, most LT female recipients are post-menopausal, and the lower estrogenic levels associated with this state have been clinically associated with higher degrees of fibrosis^[30,123]. Although in immune-

competent HCV-infected women menopause is per se frequently associated with steatosis, which is an important cofactor for disease progression^[118,124], another hypothesis is that women who require LT are the ones with genetic, virological and immunological factors that determine a more severe course of HCV-related disease, leading to LT, which in turn progresses more rapidly after LT^[117]. Moreover, female gender has been shown to be an independent negative prognostic factor for the outcome of HCV antiviral therapy after LT^[125]. Although male and female patients did not differ in HCV viral load, histology, or rate of diabetes at baseline, SVR was significantly lower in females than in males (29.5% *vs* 42.1%; $P = 0.03$). Partly explaining this unfavorable response rate, the authors found that compliance to therapy was also significantly lower in women with respect to men (43.4% *vs* 23.8%; $P = 0.001$), and that anemia was the main reason for lower adherence. On multivariate analysis, female gender ($P < 0.04$), early virological response ($P < 0.0001$), and adherence to therapy ($P < 0.0001$) were independent predictors for SVR^[126].

SPECIAL ISSUES REGARDING LIVER TRANSPLANTATION AND GENDER

Bone metabolism

Immunosuppressive medication is a major contributor to osteoporosis in the post transplant period^[127,128], and post-menopausal women are at higher risk for developing osteoporosis compared to women in the fertile age, as a consequence of decreased serum estrogen levels^[129]. The predominant deleterious effects of steroids on bone metabolism include reduced bone formation by decreasing osteoblast replication and differentiation, and increased apoptosis^[130,131]. Among calcineurin inhibitors, cyclosporine has increase bone turnover^[132], whereas tacrolimus may cause less bone loss^[133,134]. A prospective study evaluated 23 women who underwent LT, of whom 13% were peri-menopausal and 56.5% were post-menopausal, finding that in peri- and post-menopausal women, an inferior bone mass was observed in 81.2% of patients: of whom 50% diagnosed with having low bone mass and 31.2% with osteoporosis. Moreover, the postmenopausal stage was significantly associated with a decreased bone mass ($P < 0.0001$)^[135].

Risk of de novo malignancy

Aside from the risks concerning bone disease, immunosuppression increases the probability of de novo tumors^[136-138]; in a multicentric Italian study showed that the risk for some types of tumors was particularly and significantly higher in women, specifically carcinomas of tongue, all tumors of the oral cavity, and head/neck cancers^[139]. In contrast, a smaller study analyzing predictors of de novo malignancies in 534 LT recipients, did not find gender to play a role^[140].

Sexual life, fertility and pregnancy

Reproductive function is often severely compromised

in women with advanced liver disease, and is frequently characterized by menstrual irregularity, amenorrhea, and infertility in nearly half of patients^[141,142]. Etiologies of chronic liver disease which more frequently affect female patients, such as autoimmune hepatitis, may worsen during the course of pregnancy, as most diseases of autoimmune origin, with flares of disease activity reported in 7%-21% and 11%-86% of women during the gestational period and during the post-partum period, respectively^[141,143-146]. Although maternal outcomes are generally favorable, pregnancy has been reportedly the trigger for hepatic decompensation (leading to LT in some cases) and maternal death (including liver-related death), with fetal outcomes which are lower than those of the general population, but comparable to those of other autoimmune diseases^[141,143-147]. In the study by Westbrook and collaborators^[147], of 81 pregnancies in 53 autoimmune hepatitis patients, 41% took place in the context of cirrhosis, and live birth rate was significantly lower within this category. Furthermore, a serious maternal adverse event (death or need for LT) during or within 12-mo of delivery, or hepatic decompensation during or within 3-mo of delivery, occurred with 9 pregnancies (11%) and was more common in women with cirrhosis ($P = 0.028$), and patients who experienced a flare in association with pregnancy were more likely to develop hepatic decompensation ($P = 0.01$)^[147]. As flares are more frequent in patients who are not on therapy or who have had a disease flare in the year prior to conception and, pre-conception counselling and adequate gestational management are paramount.

In general, an elevated percentage of women are sexually active after LT^[148,149]. Approximately 70% of transplant recipients in a study from Brazil were reportedly sexually active after a median of 36 mo after successful LT^[150], whereas decreased libido and difficulty to reach orgasm with intercourse has been described in 26% of female LT recipients^[151]. Successful LT restores menstrual function in 97% of female patients, as well as childbearing potential^[152-154]. In general, LT leads to partial or complete normalization of both levels of sex hormones and sexual function within several months of LT^[155], with nearly 48% of women in their fertile age experiencing regular menses, 26% irregular bleeding, and 26% amenorrhea^[153], while more than 60% of peri-menopausal women reportedly experience a higher frequency of menstrual pattern disorders^[156]. In the United States only, approximately 14000 women of childbearing age are currently LT recipients, and another 500 women will undergo LT annually^[124]. The optimal timing of conception is still a matter of debate, but waiting at least 1 year after LT is generally recommended^[157]. Regarding immunosuppression, calcineurin inhibitors and steroids can be used safely, while azathioprine and mycophenolate mofetil have been associated with increased toxic effects^[158]. Pregnancy outcomes after LT are acceptable in terms of the health of the mother and of the newborn^[159], and reportedly better in comparison to those obtained after kidney transplantation, with significantly lower rates of hypertension, preeclampsia, preterm

Table 1 Key points

Several factors contribute to the unequal access to liver transplantation that penalizes women, including inadequacy of MELD score in accounting for renal dysfunction in females, the limitation of MELD score in reflecting the actual severity of liver disease and associated complications in certain clinical conditions that are more frequent in women, and the centers' increasing prevalence of policies that favor transplantation for hepatocellular carcinoma, which is more frequent in males

Different etiologies of liver disease follow a characteristic pattern of gender-related frequency, natural evolution, and response to treatment, partly owing to socioepidemiological factors as well as to phenotypical differences regarding enzymatic activity and hormonal status

Within the female population, a clear difference exists between the pre- and the post-menopausal stages, and after this turning point, the protective effect of estrogens on slowing fibrosis progression, amongst others, is lost, causing an acceleration of hepatic injury, a detrimental response to therapy, and the potential establishment of a new set of complications associated with altered fat and bone metabolism

Although long-term overall outcomes after liver transplantation are better in women, certain conditions such as renal dysfunction, hepatocellular carcinoma as an indication for transplant and recurrent hepatitis C infection are associated with worse prognosis in women with respect to men

In spite fertility and sexual activity may be curbed in advanced cirrhosis, there are numerous reports of unaffected pregnancies in this stage, while successful liver transplantation restores fertility and sexual activity in most patients, with pregnancy outcomes which are reportedly better in comparison to those obtained after kidney transplantation

MELD: Model for end-stage liver disease.

deliveries, and birth of neonates small for their gestational age^[160].

In a study from Vienna assessing 39 deliveries and 40 live births^[161], the mean time from organ transplantation to delivery was 67.6 ± 47.2 mo. A meta-analysis on 450 pregnancies in 306 LT recipients showed that although the rates of pre-eclampsia (21.9%), caesarean section delivery (44.6%), and preterm delivery (39.4%) were higher than the rates for the US general population (3.8%, 31.9%, and 12.5%, respectively), the post-LT live birth rate (76.9%) was higher than the live birth rate for the US general population (66.7%), and the post-LT miscarriage rate (15.6%) was lower than the miscarriage rate for the general population (17.1%)^[162].

Quality of life after liver transplantation

In a German cross-sectional, single-center study evaluating the quality of life in 281 LT recipients^[163], similar results were observed between male and female subjects, whereas in another study analyzing gender differences after HCV-related LT, however, it emerged that male subjects score significantly higher on physical role functioning and physical activity compared with females, whereas women had reportedly better quality of life compared to males with regard to the emotional state and mental health 1-year after LT^[164].

CONCLUSION

Important gender differences exist regarding etiologies of liver disease, severity of the course of these diseases, and on outcomes after LT. Unfortunately, access to LT is still governed by an imperfect allocation system, currently based on MELD score, which includes systematic biases against women, and is also hampered by factors that are not adequately taken into account by MELD score, doubly penalizing female gender. A delayed access to LT wait-listing and subsequently to LT due to renal dysfunction underestimation, is a determinant factor that has an impact on post-transplant renal function as well. Being generally smaller than men, organ allocation decisions

generally favor children as recipients of small organs, and men as recipients of large organs, conditioning a longer waiting time for an organ in adult women.

Throughout a women's life, profound hormonal changes also determine the natural course of diseases; while estrogens may protect against inflammation and fibrosis during the fertile age, the post status takes a high toll on disease progression both before and after LT, and may be further complicated by obesity, NASH, NAFLD, and other components of the metabolic syndrome. The above are summarized in Table 1 (Key points). It is therefore ever clearer that special attention should be paid to the integral management of women during the different life periods, and with respect to special situations regarding natural evolution and risk factors for liver disease, as well as to those affecting post-transplant outcome.

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