Sexual Function, Fertility and Pregnancy in Liver Disease and After Liver Transplantation

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Overview

Sexual dysfunction is characterized by disturbances in sexual desire and in the psychophysiological changes associated with the sexual response cycle in men and women. It is a common problem in both sexes, reportedly affecting from 10–50% of men and 25–60% of women [1]. Despite the potential impact of these disorders on quality of life, epidemiological data are relatively scant, and even less information has been reported on liver transplant recipients.

32.1 Sexual Dysfunction in Men with Liver Disease

Erectile dysfunction is the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse, and it can result from various causes. The hormone situation in male patients with end-stage liver disease can prompt hypogonadism and signs of feminization [2]. Few studies have been conducted on the changes occurring in the hypothalamic–pituitary–gonadal axis in male patients with cirrhosis. The liver influences the endocrine function of the testis, interacting with at least two mechanisms: (1) determining the levels of free testosterone (the biologically most active fraction) via the synthesis of sex hormone-binding globulin

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(SHBG) and albumin and (2) influencing the endocrine homeostasis of sex hormones by converting androgens into estrogens under the effect of aromatase, and the deactivation of sex hormones by specific enzymes (approximately 70% of the total catabolism). Testosterone is converted in the liver into androstenediol, androsterone, and androstenedione by a specific hydroxysteroid, and into dehydrogenases, etiocholanolone, or dihydrotestosterone by a specific reductase (5α-reductase). Imbalance in the hormone homeostasis mechanism therefore leads to sexual dysfunction [3].

One in two male patients with cirrhosis has a reduced spermatogenesis and peritubular fibrosis [4]. These alterations are more pronounced in patients with higher Child-Pugh scores [5, 6]. It has also been reported that sexual activity correlates inversely with Model for End-Stage Liver Disease (MELD) scores and that MELD scores correlate with erectile dysfunction [7, 8].

In addition to an impaired hormone homeostasis, the use of medicines in patients with complications of cirrhosis, such as ascites, may influence their sexual function. Gynecomastia and impotence are exacerbated by spironolactone, a receptor antagonist of aldosterone and testosterone, which reduces testosterone levels and slightly increases estradiol levels [8]. Beta-blockers used as prophylactic therapy to prevent variceal bleeding in portal hypertension also have a role in sexual dysfunction: their mechanism of action (an intrinsic-sympathomimetic activity) can lead to erectile dysfunction [9].

Non-organic erectile dysfunction—also known as psychogenic or adrenaline-mediated erectile dysfunction—has yet to be studied in depth, but it is an important factor to consider when assessing and managing males with chronic disease. Stress, depression, and disease can generate anxiety about the ability to achieve and maintain an erection before or during sexual intercourse, giving rise to psychogenic erectile dysfunction [10]. Sarcopenia, jaundice, and hepatic encephalopathy can lead to a loss of self-image and difficulties in the sphere of sexuality.

32.2 Sexual Dysfunction in Women with Liver Disease

Anovulation is a common problem in women with cirrhosis, with secondary amenorrhea, oligomenorrhea, or erratic episodes of metrorrhagia. Hormone balance is impaired in cirrhosis and levels of testosterone, estradiol, prolactin, and luteinizing hormone (LH) may differ significantly from those of normal subjects. Amenorrhea is not always related to the duration or severity of liver disease, and it may arise from hypothalamic–pituitary dysfunction occurring at any stage [11, 12].

In a study by Giard et al. on women under 46 years old on the waiting list for liver transplantation (LT), 53% reported regular menstrual cycles, 27% irregular and unpredictable bleeding, and 20% amenorrhea. Their liver function did not correlate with any menstrual pattern abnormalities. Sexual dysfunction (defined as a reduced sexual frequency and satisfaction) was more prevalent in these women than in men with end-stage liver disease. Older age and more severe liver disease were related to lower sexual frequency and satisfaction [13] (Table 32.1).

Table 32.1 Factors that can cause sexual dysfunction before liver transplantation

Hormone imbalance due to cirrhosis	Hypogonadism Reduced spermatogenesis and erectile dysfunction Amenorrhea
Iatrogenic factors	Diuretics B-blockers Corticosteroids
Etiology of liver disease	Alcohol Viral Autoimmune Cholestatic
Psychological factors	Depression Anxiety

32.3 Sexual Dysfunction by Liver Disease Etiology

32.3.1 Alcoholic Liver Disease

Numerous studies have been performed on sex hormone disturbances in men with chronic alcoholic and non-alcoholic liver disease, but very few in women. Chronic alcohol abuse causes disturbances in the hormone status and reproductive performance of women [12]. Becker et al. examined the effect of ethanol and liver dysfunction on the menstrual cycle, serum sex hormone concentrations, and hepatic estrogen receptors in women. In premenopausal females, alcohol consumption increased the frequency of menstrual disturbances, abortions, and miscarriages, while infertility was infrequent [14]. When acute and chronic alcohol intake are compared, only minor effects on pituitary–gonadal hormones are described in premenopausal women in the event of acute intake [14], while chronic alcohol abuse leads to reduced concentrations of sulfated steroids, and these changes may be seen before severe liver dysfunction has appeared [14].

Sexual dysfunction due to alcoholic liver disease in women leads to an earlier onset of menopause than in normal controls [14]. Among men with liver disease, the clinical signs of hypogonadism are more pronounced in alcoholic patients because of the direct effect of ethanol on the testes [7, 10, 15]. The primary gonadal damage typical of alcohol abuse gives rise to a form of primary hypogonadism with increased levels of the pituitary gonadotropins follicle-stimulating hormone (FSH) and LH (hypergonadotropic hypogonadism) [7].

Liver cirrhosis affects the function of the Leydig cells responsible for testosterone synthesis, even when plasma testosterone levels are normal and irrespective of the etiology of the underlying liver disease [16]. Some patients' apparently normal serum testosterone levels are actually due to an increased output of LH (subclinical primary hypogonadism), and an altered response to the administration of human chorionic gonadotropin has been demonstrated even in cases with normal hormone levels [2, 5, 16].

It is alcohol abuse per se, not the liver disease associated with it, that is responsible for the impotence, loss of libido, and testicular atrophy commonly seen in chronically alcoholic men. Recent studies have suggested that prolonged alcohol

abstinence can lead to a spontaneous recovery of normal sexual function unless testicular atrophy has already occurred [17].

32.3.2 Viral Hepatitis

32.3.2.1 Hepatitis B Virus

Irregular menstruation patterns have been reported in female patients with hepatitis B virus (HBV)-related liver disease, the consequence of which might be an impaired reproductive rate or infertility [18]. The hypothesis to explain this picture focuses on the immune system derangement seen in HBV populations: patients with an intact reproductive function reveal a depressed T-cell immunity whereas patients with a history of miscarriage show diverse changes in lymphocyte subpopulations, and—in cases of infertility—severe T-cell-component depression, with a decrease in total T-cells and T-helper cells and active lymphocytes [18].

The pathophysiology behind erectile dysfunction in patients with chronic viral liver disease has yet to be fully elucidated. Kim et al. [19] found significant differences in serum albumin levels between patients with and without erectile dysfunction. A correlation between serum albumin and erectile dysfunction had previously been reported by Toda et al. [20]. A lower albumin production might influence the ratio of albumin bound to free testosterone, which is associated with sexual desire and sleep-related erection as well as a cause of water retention and loss of muscle volume, with a consequent deterioration in patients' physical functioning [21].

By reducing sexual desire and physical activity, depression can also cause erectile dysfunction. Chronic infection with HBV is associated with several psychiatric disorders, including anxiety and depression, and there is a significant link between depression and erectile dysfunction in patients with HBV-related chronic liver disease. Depression may also be a side effect of medication for chronic HBV infection, including interferon (IFN) [22].

32.3.2.2 Hepatitis C Virus

Several recent studies reported a significant relationship between hepatitis C virus (HCV) infection and female reproductive status, highlighting the protective effect of a fertile hormone status against the progression of fibrosis [23–25]. Specifically, it was found that HCV+ women had significantly lower levels of the anti-Mulleran hormone than age-matched uninfected controls or women with HBV+, and this was significantly associated with a higher miscarriage rate in the former [26]. Anti-Mulleran hormone levels were also found significantly lower in HCV+ women than in age-matched healthy controls. These findings point to a specific connection between HCV infection, ovarian function, and reproductive efficiency, suggesting that the premature ovarian senescence observed in women who are HCV+ (as indicated by an early, significant decline in anti-Mulleran hormone levels) has a profound effect on their reproductive function [26]. No relationship has emerged with a lower desire for pregnancy among women with HCV, however, and a recent study showed that female patients with chronic viral liver disease desire children just as much as women in the general population [27].

Several studies found an impact of HCV infection on patients' sexual health and identified a number of potential determinants. Chronic HCV infection may be associated with three distinct patterns of sexual dysfunction, namely, pre-cirrhotic sexual impairment; cirrhosis-induced sexual decline; and IFN-associated sexual difficulties [28]. Pre-cirrhotic sexual impairment is linked to extrahepatic disease processes and psychological discomfort. Cirrhosis-induced sexual decline is associated with the progression of liver fibrosis. IFN-associated sexual difficulties probably reflect the combined effects of depression and viral pathophysiology [28]. This picture would suggest that extrahepatic pathophysiological processes and psychological distress both contribute to the sexual decline seen in the early stages of HCV infection. HCV RNA and, in some cases, the RNA negative strand (which is a replicative form of the virus) have been detected in patients' central nervous system microglia and cerebrospinal fluid [29, 30]. The fact that hepatitis C patients report a more severe impairment in the sphere of sexuality, relating to desire, drive, and satisfaction (which are based on higher cortical processes than other sexual subdomains, such as erection, ejaculation, and orgasm, which rely largely on reflexes) might point to disturbances in the neural circuits of the prefrontal cortex, the limbic system, the hypothalamus, and the ventral striatum due either to direct effects of the virus or to HCV-induced neuro-inflammation [31–36]. Be that as it may, the pathogenesis of HCV-related sexual dysfunction is multifactorial, with both physical and psychological components. Although depressed individuals frequently suffer from loss of sexual interest, reduced libido, and impaired sexual functioning, findings to date suggest that depression in HCV patients, though important, is not enough to explain the full range and severity of their impairment [36].

32.3.3 Cholestatic Liver Disease

32.3.3.1 Primary Sclerosing Cholangitis (PSC)

PSC is usually diagnosed during a period of peak fertility and childbearing [37]. A diagnosis of PSC in women of reproductive age often raises concerns regarding its impact on their fertility and pregnancy, and vice versa. Although studies on fertility and pregnancy in PSC are limited, the available data suggest that PSC has no specific detrimental impact on women's fertility and chances of pregnancy [38].

32.3.3.2 Primary Biliary Cholangitis (PBC)

The majority of women with PBC are diagnosed at post-menopausal age [39]. Histological evidence of PBC may appear much earlier, however, and recent reports indicate that up to 25% of female PBC patients are now diagnosed in their reproductive age [40, 41]. Younger women of childbearing age tend to be more symptomatic than older women with PBC [42]. That said, in the largest population-based study on PBC to date, the disease was not associated with any decline in fertility; and this finding was replicated in a subsequent study. Though the literature on this topic is limited to small cohort studies and case-control studies, no significant or severe risk to fertility has been found thus far in women diagnosed with PBC [42].

Table 32.2 Sexual dysfunction by etiology of liver disease and sex before liver transplantation

	Male	Female
Alcoholic liver disease	Primary hypogonadism Testicular atrophy Loss of libido	Menstrual disorders More frequent abortions Loss of libido
HBV	Decline in physical functioning Decreased albumin production Depression	Menstrual disorders Depression of T-cell-mediated immunity Depression
HCV	Loss of sexual desire Neural inflammation Depression	Lower anti-Mulleran hormone levels High miscarriage rate Premature ovarian senescence
Cholestatic liver disease	Hormone imbalance due to cirrhosis	Hormone imbalance due to cirrhosis
Autoimmune liver disease	Hormone imbalance due to cirrhosis	Oligomenorrhea

32.3.3.3 Autoimmune Hepatitis (AIH)

In spite of the frequently associated oligomenorrhea, pregnancies in patients with AIH are becoming more common as a result of their better clinical management [43]. As in all cirrhotic patients with severe disease, patients may have an altered hormone homeostasis (hypothalamic–pituitary axis), and AIH is also frequently associated with other endocrinopathies. Flares occur during pregnancy in 7–33% of cases, and postpartum in 11–86% of women with AIH. The majority of these flares can be controlled by incrementing the patient's immunosuppressant treatment [43, 44] (Table 32.2).

32.4 Liver Disease and Pregnancy

32.4.1 Pregnancy in Women with Liver Disease

Women with liver disease can become pregnant. An interesting example comes from a case report from Ferrarese and Burra [45] concerning a patient with Alagille syndrome (AGS), an inherited autosomal dominant multisystem disorder with protean clinical manifestations. In this particular case, the patient delivered at 38 weeks of gestation with no complications for the newborn or mother. Successful pregnancies are unusual in AGS, however, as in other chronic liver diseases, due to a lower fertility, voluntary abortions, and miscarriages. Judging from the few reported cases of successful pregnancy in AGS, there are several issues to consider before attempting a pregnancy. These include the severity of the liver disease, and portal hypertension (which could be exacerbated by pregnancy), of cardiac dysfunction, and especially of pulmonary hypertension, and the various phenotypic manifestations in the newborn [45].

32.4.1.1 Viral Hepatitis

HBV

In women with chronic HBV infection, immunological changes typical of pregnancy may cause an increase in HBV DNA levels, while ALT remain normal or near

normal. Mild exacerbations may occur after delivery too [46, 47]. In clinical practice, women who are HBV+ carriers should be counselled regarding pregnancy both on and off treatment. In all cases, the indications to treatment according to current recommendations should be considered and discussed with the patient [48]. Treatment can be delayed when fibrosis is mild or absent, and women already receiving treatment may be able to stop antiviral drugs [49]. When treatment is indicated, tenofovir is the best choice. Women who become pregnant while taking entecavir or adefovir should be switched to tenofovir if continued treatment is indicated. The vertical transmission of HBV infection is prevented by administering vaccines and anti-HB immunoglobulins to the newborn within 12 h after delivery [50].

HCV

The natural history of HCV-related liver disease in pregnant women and their offspring is not fully understood. Pregnancy does not seem to modify the natural course of HCV-related liver disease: women are generally asymptomatic during pregnancy, and a significant reduction in ALT levels has been reported, with a rebound postpartum [51, 52]. There is also an increase in HCV-RNA towards the end of the pregnancy in most HCV-infected pregnant women, though several studies monitoring viral load monthly found HCV-RNA stable throughout the pregnancy in chronic HCV carriers with no biochemical activity, whereas viremic flares occurred in those with biochemical activity [51, 52]. Retrospective data suggest a significantly higher incidence of intrahepatic cholestasis of pregnancy in HCV-infected pregnant women than in controls. Chronic hepatitis C can lead to a vertical transmission of HCV, while it only marginally influences the course of pregnancy and seldom induces spontaneous abortion. The global HCV vertical transmission rate is relatively low and estimated to affect only 3–5% of infants born from HCV+ mothers [53, 54].

32.4.1.2 Autoimmune Hepatitis

In the case of pregnancy at the time of presentation of "acute"-onset AIH, the liver disease may take a fulminant course and the fetus has little chance of survival [55]. Generally speaking, women who achieve disease remission, and have no cirrhosis with portal hypertension, have a good chance of a successful pregnancy [56]. Gestation has a beneficial effect on patients' immune status, enabling a reduction in their maintenance immunotherapy. This is due to several factors, including a physiological increase of serum cortisol [57, 58]. In clinical practice, the dosage of steroids needed to maintain remission should therefore be reduced in the case of pregnancy, although flares may occur during the course of the pregnancy in up to 21% of cases. The probability of flares is highest after delivery, however, with an incidence as high as 40%. Ursodeoxycholicacid is safe and well tolerated during pregnancy [59].

32.4.1.3 Primary Sclerosing Cholangitis (PSC)

PSC has an incidence of around 0.9–1.3 per 100,000 population per year and a prevalence of around 8.5–14.2 per 100,000 in Northern Europe and the United States. Up to 80% of PSC patients have concurrent inflammatory bowel disease [60]. Fertility does not seem to be reduced in patients with PSC, and pregnancy is

possible in young female patients. No strong association has been found between the onset of PSC and previous perinatal events including newborn birth length, breastfeeding, and the majority of maternal medical complications [61].

32.4.2 Pregnancy-Related Liver Disease

Intrahepatic cholestasis of pregnancy: this develops in the last trimester and rapidly resolves after delivery. It is characterized by severe pruritus, associated with an increase in serum bile acids and aminotransferases. The symptoms and biochemical abnormalities rapidly disappear after delivery but may recur in subsequent pregnancies and with the use of hormonal contraception. Potential complications of the condition include premature delivery, respiratory complications, and intrauterine death [62].

A*cute fatty liver of pregnancy*: this involves a microvesicular fatty infiltration of hepatocytes and it is a common cause of liver failure in pregnancy. It is a late-gestational complication, often occurring between weeks 28 and 40. It is a rare disorder, affecting from 1:7000 to 1:16,000 pregnancies, but it is a medical and obstetric emergency. Risk factors are nulliparity, preeclampsia, multiple gestation, pregnancies with a male fetus, and a low BMI [63, 64].

HELLP syndrome: the hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is associated with endothelial cell injury and microangiopathic platelet activation and consumption. It occurs in 4–20% of cases of preeclampsia [65]. The disorder can be diagnosed antepartum (between 27 and 30 weeks of gestation in 70% of cases) or postpartum. Risk factors are advanced maternal age, multiparity, and Caucasian ethnicity. Hypertension and proteinuria are evident in up to 85% of cases [66]. Because of the hemolysis, high serum unconjugated bilirubin and lactate dehydrogenase are frequent findings as well as a moderate rise in liver enzymes [67]. Complications include disseminated intravascular coagulation, pulmonary edema and placental abruption. The perinatal mortality rate ranges from 6 to 70%, while maternal mortality is 1% [68]. Once HELLP syndrome develops, the only definitive treatment is delivery of the fetus. If the gestational age is between 24 and 34 weeks, corticosteroids are usually administered to promote fetal lung maturity, and delivery should be considered 24 h afterwards [65].

32.4.3 Liver Disease During Pregnancy

32.4.3.1 Acute Viral Hepatitis

The most common cause of jaundice in pregnancy is acute viral hepatitis. The incidence of hepatitis in pregnancy varies greatly around the world, depending on levels of hygiene, sanitation, and socio-economic status [69].

Hepatitis A virus is the most common cause of acute viral hepatitis in the general population, but its occurrence during pregnancy has been under-reported.

Hepatitis A is not associated with a severe outcome during pregnancy and vertical transmission is very rare [70].

HBV infection is not associated with any increased fetal mortality or congenital malformations, though it can cause spontaneous abortion in the first weeks of pregnancy [71]. Acute HBV infection in pregnancy has a higher rate of vertical transmission, which usually occurs during delivery due to the newborn's exposure to cervical secretions and maternal blood [72].

HCV infection has rarely been reported during pregnancy and is limited to high-risk groups, such as intravenous drug users. The frequency of acute HCV infection during pregnancy is estimated at between 0.4 and 6% [73]. HCV infection can be transmitted vertically (the risk being from 3 to 5%), but there is no evidence of increased transmission through breastfeeding [74]. Antiviral treatment is contraindicated due to the teratogenic effects of the drugs available until recently, while no data are available as yet for the new IFN-free regimens in this setting [75].

Hepatitis E virus (HEV) is responsible for major outbreaks of acute hepatitis in developing countries. It is enterally transmitted and clinical manifestations are similar to other forms of viral hepatitis, but in pregnant women there is a higher risk of fulminant hepatitis (25% mortality rate) [76]. A recent study compared maternal and fetal outcomes in pregnant women with acute hepatitis caused by HEV and other viruses: fulminant liver failure was more common and maternal mortality was higher for HEV-infected women than for women without any viral infections. Women with HEV infection were also at higher risk of intrauterine fetal death [77].

32.4.3.2 Budd Chiari Syndrome (BCS)

This is a rare disease caused by obstruction of the hepatic venous outflow due to thrombosis of the hepatic veins or of the suprahepatic portion of the inferior vena cava, leading to sinusoidal congestion, ischemic liver damage, and portal hypertension [78]. Patients usually have one or more risk factors for venous thromboembolism. In pregnancy, the levels of coagulation factors VII and VIII, von Willebrand factor, and fibrinogen are increased, while free protein S levels are reduced and increased levels of plasminogen activator inhibitor-1 and -2 (the latter synthesized by the placenta) reduce fibrinolytic activity. These changes shift the hemostatic balance towards hypercoagulability, which persists for up to 8 weeks after delivery [79]. It is therefore hardly surprising that pregnancy can trigger or exacerbate the vascular liver diseases in which thrombophilia often plays a major part. In pregnancy, the clinical presentation of BCS is often fulminant, and the associated mortality rate is high [80]. BCS is managed differently in pregnancy because the options used for other women, such as vitamin K antagonists, are contraindicated due to a risk of fetal hemorrhage and teratogenicity. A stepwise treatment is recommended, starting with twice-daily low-molecular-weight heparin, followed by transjugular-intrahepatic-portosystemic-shuntin failures or relapses. LT is an option [81].

32.5 Sexual Function After Liver Transplantation

Successful LT leads to improvements in sex hormone disturbances in both men and women, but post-LT medication—including immunosuppressants—may interfere with hormone metabolism.

32.5.1 Male Recipients

32.5.1.1 Medication

Among the types of medication that may be involved in the pathogenesis of erectile dysfunction in male patients, antihypertensives and corticosteroids should also be borne in mind [82]. The role of immunosuppressants is still not clear. In the early post-transplant period, up to a month after surgery, plasma levels of total and free testosterone may be significantly reduced with respect to a patient's levels before the procedure [2, 83]. The same situation has been seen after kidney transplantation too, which coincides with a drop in Sex-hormones-binding-protein levels. This has been attributed to the high doses of immunosuppressants administered in this phase, including both corticosteroids and calcineurin inhibitors such as cyclosporin A [84] and tacrolimus. The pathogenesis of erectile dysfunction is multifactorial, including hypogonadism and treatment with calcineurin inhibitors. It has been demonstrated that calcineurin is strongly expressed in the testis [85], and it is involved in the cell mechanisms fundamental to a normal sperm function [86]. An altered spermatogenesis might also explain the increased FSH levels encountered especially in the first 12 months after LT.

Several studies have emphasized the potential impact of sirolimus on male gonadal function [87–89]. This was first reported as a significant decrease in free testosterone and a significant increase in LH and FSH levels in heart transplant patients treated with sirolimus. A recent review [90] of all published studies on transplant patients who received mammalian target of rapamycin inhibitors showed consistent evidence of sirolimus-related gonadal function being suppressed and FSH and LH concentrations being increased. In a recent cross-sectional study, [83] despite lower total testosterone levels and higher FSH and LH levels, there was no significant difference in sexual function scores between patients treated with sirolimus and a control group. Therefore, it seems that immunosuppression is one aspect of transplantation that should be decided carefully to strike the right balance of benefits for the graft and quality of life [84].

32.5.1.2 Hormone Homeostasis

The proportion of sexually inactive men reportedly decreased from 29% before LT to 15% afterwards, but the proportion of men with erectile dysfunction remained unchanged. The absence of sexual activity after LT was associated with pretransplant sexual inactivity, age, cardiovascular disease, and use of diuretics, anticoagulants, statins, and treatment for diabetes. Cardiovascular disease, post-transplantation diabetes, alcohol abuse, antidepressants, and angiotensin II receptor blockers were all associated with erectile dysfunction after LT [91].

A study by Burra et al. on patients before and after transplantation at the Multivisceral Transplant Unit of Padua University Hospital showed that patients with liver cirrhosis awaiting LT had significantly higher levels of prolactin and sexual-hormones-binding-protein than patients with a liver transplant. Sexual dysfunction also correlated with old age, whereas after LT it was more associated with depression. So sexual dysfunction was confirmed for both men and women with liver cirrhosis, but it was surprisingly persistent after LT, with depression being the major risk factor [1].

Other studies have since shown that even patients with marked hypogonadism before LT frequently achieve a functional recovery of their hypothalamic–pituitary–testicular axis in terms of testosterone and prolactin secretion, and regained fertility [92, 93]. Some authors have found, however, that—despite a marked reduction in sex-hormones-binding-protein—the normalization of free testosterone levels derives from a greater output of gonadotropins, especially LH, already in the first 12 months after LT (subclinical primary hypogonadism) [94, 95]. This anomaly has been confirmed in hypogonadal nephropathic patients undergoing kidney transplantation as well [96]. In addition, the rise in free testosterone levels after LT still fails to reach normal levels in more than one in three patients [82, 97, 98], with a concomitant increase in LH (hypergonadotropic hypogonadism).

32.5.2 Female Recipients

32.5.2.1 Fertility

Women achieve normal menstrual function and fertility a few months after LT, and the recommendation for women of reproductive age who undergo LT is to monitor the timing and pattern of menstruation, sexual activity, contraception, and the incidence of pregnancy and gynecological disorders. In the year before LT, 42% of women reported regular menstrual cycles, 28% reported irregular and unpredictable bleeding, and 30% reported amenorrhea; after transplantation, 48% experienced regular menses, 26% irregular bleeding, and 26% amenorrhea [99]. Women currently account for one in three liver transplant recipients, and approximately a third of them are of reproductive age (18–49 years old). The first successful pregnancy following LT occurred in 1978, with excellent maternal and fetal outcomes. Numerous studies have been published [100–111], and there are registries for pregnancies after LT, but no randomized controlled trials have been conducted to date, and much of the evidence regarding drug safety during pregnancy comes from animal studies. Thus, although efforts have been made to develop evidence-based management strategies, more work needs to be done in this setting [112].

In one study by Burra et al. on women who underwent LT at the Multivisceral Transplant Unit in Padua, psychological status seemed to play a key part in sexual dysfunction after LT. Depression was the main risk factor for sexual dysfunction persisting after LT in both sexes. As for the role of patients' previous liver disease in determining any sexual dysfunction after LT, female patients who underwent the

Table 32.3 Factors that can cause sexual dysfunction after liver transplantation

Hormone imbalance	Hypogonadism (mostly in the first year after LT)
Iatrogenic factors	Immunosuppressants Therapy for possible complications after LT
Complications after LT	Recurrence of liver disease Diabetes Hypertension Rejection
Psychological factors	Depression Anxiety regarding sexual performance

procedure for virus-related liver disease had a more severe sexual dysfunction than those transplanted for other causes of liver disease. Previous studies also found HCV to be a major determinant of both clinical and psychological outcomes after LT, and it has been associated with a poor subsequent quality of life [113–115].

32.5.2.2 Contraception

Contraception is needed for women who undergo LT. Such ineffective methods as coitus interruptus and abstinence cannot be recommended [116]. The safest methods for both birth control and to prevent infectious disease are barrier methods, which also have the advantage of avoiding drug interactions as well as having low failure rates [117].

Intrauterine devices are very effective in the general population but may increase the risk of infection [118], and it has been suggested that they may be less effective in immunosuppressed patients [119, 120]. As concerns oral or transdermal contraceptives, the same contraindications apply as in the general population (history of myocardial infarction, stroke or deep vein thrombosis, and migraine with focal aura). Since these contraceptives are metabolized by the hepatic cytochrome P4503A4 system, drug-to-drug interactions may also be a concern—especially with cyclosporine and tacrolimus, which are both metabolized by this same enzyme [121]. Oral contraceptives should be used with caution after LT, frequently monitoring liver function, and only in recipients with a graft function that has remained stable for at least 6–8 months, and no other contraindications [121, 122] (Table 32.3).

32.5.2.3 Pregnancy

Maternal Complications After Liver Transplantation

With the return of normal sexual function, women who have successfully undergone LT can conceive as early as 1 month later [107, 123]. The most favorable factors for a good outcome of the pregnancy are: a stable graft function, stable immunosuppression, and no hypertension prior to conception [107, 124–126]. If a patient manifests her informed intention to become pregnant, it is fundamental to optimize her immunosuppression, graft status, and general heath [125]. On this premise, the American Society of Transplantation recommends that pregnancy be considered in women who undergo LT providing there is no sign of rejection within the year before the intended conception; graft function is adequate and stable; there are no

acute infections capable of affecting fetal growth and well-being; and maintenance immunosuppressants are administered in stable doses [127]. In short, though nothing is said about the timing of conception after LT, waiting 1–2 years is generally considered a good idea [127]. An important issue concerning pregnancy in women who have undergone LT concerns their immunosuppression regime and the risk of rejection. The question is how to strike the right balance between the teratogenic risk of the drugs and the risk of graft rejection. The reported incidence of rejection in pregnancy varies considerably (from 0 to 20%), as opposed to approximately 2–3% for women who do not become pregnant after LT [103, 107, 108]. An important issue here concerns pregnant women deliberately suspending their immunosuppressants (which reportedly accounts for the above-mentioned higher rejection rate), and episodes of rejection are generally reversible with steroid boluses and a return to adequate immunosuppressive therapy [128]. It is fundamentally important to adequately inform women with a liver transplant during any pregnancy to avoid them suspending their drugs under their own initiative and ensure that they continue to adhere to their appropriate therapy.

Fetal Complications

Most fetal complications—including spontaneous abortion, preterm birth, intrauterine growth restriction, and fetal distress—are statistically more common in transplant recipients than in the general population [129, 130], while the incidence of congenital anomalies is apparently comparable [126]. Some authors have suggested that the higher risk of preterm birth might be partly due to episodes of graft rejection and early-onset pre-eclampsia, but this has yet to be confirmed [107] (Table 32.3).

32.5.2.4 Immunosuppressants and Pregnancy

Calcineurin Inhibitors

These drugs (cyclosporine and tacrolimus) have not been definitively associated with teratogenesis. Fetal malformation rates are much the same for pregnancies in women who were or were not taking this type of medication [104]. Initial reports of intrauterine growth restriction, spontaneous abortion, and premature births were only associated with high doses of these drugs [131] and not confirmed in all studies. In patients with a liver transplant, it is important to frequently monitor renal function and drug concentrations in the blood, especially since cytochrome 450 is inhibited during pregnancy (and this can lead to an increase in tacrolimus levels).

Steroids

Metabolized by placental 11-hydroxygenase, steroids can cross the placenta with a blood ratio of approximately 10:1, so the fetus is exposed to about 10% of the maternal dose [132]. Steroids are often used as immunosuppressants after LT but also to treat liver disease during pregnancy (autoimmune disorders) or rejection after LT, and to induce fetal lung maturation when there is a risk of pre-term delivery [133].

Whatever the reason for taking them, steroids can complicate pregnancy with the side-effects observable in any patient (high infectious risk, osteopenia, hypertension, hyperglycemia, and cataracts), and they can exacerbate gestational diabetes [134–136].

Azathioprine

Azathioprine (AZA) apparently has no teratogenic effects. It crosses the placenta but the fetus does not have the enzyme needed to convert it into its active form. The issues with this drug mainly concern oncogenic risks. During pregnancy and breastfeeding [107], AZA seems to be associated with a higher risk of growth retardation [137, 138]. Infants exposed to AZA in early pregnancy (including pregnancies in organ transplant recipients) may be at a moderately increased risk of congenital malformations, and ventricular/atrial septal defects in particular. There is also a greater risk of growth restriction and preterm delivery, but it is not clear whether these complications might be partly due to the severity of the mother's illness [139]. Because of the potential for carcinogenesis and the unknown long-term effects of fetal immunosuppression, AZA should be withheld if possible; if not, the AZA dose should be reduced at 32 weeks of gestation [139]. An interesting case report from Loreno et al. was regarding a 33-year-old woman who had undergone liver transplantation for Caroli's; 2 years after transplantation, the patient experienced de novo HBV hepatitis. Lamivudine treatment was started and clearance of HBsAg was documented 1 year later. Four years after starting antiviral treatment, the patient became pregnant despite the risk of teratogenic effects; lamivudine, cyclosporine, and azathioprine were not discontinued for risk of break-through hepatitis and acute or chronic rejection. The course of gestation was uneventful and a caesarean section was performed after 36 weeks. The newborn infant was a healthy male weighing 3080 g and measuring 50 cm [140].

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) blocks de novo purine synthesis in T and B lymphocytes, and it has been associated with teratogenic risks. These include developmental toxicity, intrauterine death, and malformations, even when MMF is apparently administered at the recommended clinical doses based on body surface area [141]. Exposure to MMF during early pregnancy was found associated with a higher incidence of structural malformations in the study by Sifontis et al. [142]. As a result of this significant teratogenic risk, the Food and Drug Administration in the USA has issued a boxed warning concerning the risk of first-trimester fetal loss and congenital malformations [143]: the drug is now classified as US FDA category D medication and should not be used during pregnancy.

Mammalian Target of Rapamycin (mTOR) Inhibitors

Evidence is still scarce regarding the use of sirolimus and everolimus during pregnancy after LT, and they are generally contraindicated in pregnancy. They should also be discontinued at least 12 weeks before attempting conception, switching to a calcineurin inhibitor for the duration of the pregnancy. When weighing the risks for

the fetus, there is still a great deal of ambiguity about whether sirolimus is intrinsically teratogenic, and it is therefore contraindicated in this setting [144–147].

32.5.2.5 Breastfeeding

Breastfeeding is strongly recommended by pediatric associations as the sole diet for the newborn at least until they are 6 months old [148] and should then be gradually reduced over the 6 months thereafter as the infant's diet is extended. This reduces the incidence of allergies, celiac disease, infectious diseases, diarrhea, and colitis in children [147]. The doses of immunosuppressants used during breastfeeding are lower than during gestation. While it is important to avoid MMF during pregnancy due to its confirmed teratogenic effects (miscarriages and fetal malformations), there are no studies describing its influence during breastfeeding in humans [149].

Tip

- The liver has a fundamental role in sex hormone homeostasis in both males and females, and cirrhosis disrupts these mechanisms. Like all chronic diseases, cirrhosis also leads to psychological dysfunctions, and sexual dysfunction is the result of the combination of these two elements
- Despite a return to a normal hormone balance, men's and women's sexual function may not always improve after LT due to psychological and pharmacological factors.
- Pregnancy after LT is feasible, even in women with persistent underlying liver disease, though acute liver disease may complicate the pregnancy.
- The outcome of a transplant should always be assessed from a multidisciplinary perspective. While considering graft function on the one hand, it is important on the other hand to assess all aspects of a patient's life and their overall physical and psychological well-being.

32.6 Conclusion

The liver has a fundamental role in sex hormone homeostasis in both males and females, and cirrhosis disrupts these mechanisms. Like all chronic diseases, cirrhosis also leads to psychological dysfunctions, and sexual dysfunction is the result of the combination of these two elements. Sexual dysfunction in cirrhosis has different etiologies, depending on the primary liver disease, and different outcomes after liver transplantation. Despite a return to a normal hormone balance, men's and women's sexual function may not always improve after LT due to psychological and pharmacological factors. Pregnancy after LT is feasible, even in women with persistent underlying liver disease, though acute liver disease may complicate the pregnancy. The guidelines recommend waiting at least 1–2 years before conceiving, ensuring a good graft function and optimal, stable levels of immunosuppression. Breastfeeding is also possible at no risk to the newborn. The fundamental issue is to prescribe appropriate and adequate immunosuppressive therapy in this setting.

The outcome of a transplant should always be assessed from a multidisciplinary perspective. While considering graft function on the one hand, it is important on the other hand to assess all aspects of a patient's life and their overall physical and psychological well-being (Tables 32.1, 32.2, and 32.3).

References

1. Burra P. Sexual dysfunction after liver transplantation. Liver Transpl. 2009;15(Suppl 2):S50–6.
2. Foresta C, Schipilliti M, Ciarleglio FA, Lenzi A, D'Amico D. Male hypogonadism in cirrhosis and after liver transplantation. J Endocrinol Investig. 2008;31(5):470–8.
3. Tadic SD, Elm MS, Subbotin VM, Eagon PK. Hypogonadism precedes liver feminization in chronic alcohol fed male rats. Hepatology. 2000;31(5):1135–40.
4. Plaud JJ, Dubbert PM, Holm J, Wittrock D, Smith P, Edison J, et al. Erectile dysfunction in men with chronic medical illness. J Behav Ther Exp Psychiatry. 1996;27(1):11–9.
5. Karagiannis A, Harsoulis F. Gonadal dysfunction in systemic diseases. Eur J Endocrinol. 2005;152(4):501–13.
6. van Thiel DH, Gavaler JS, Spero JA, Egler KM, Wright C, Sanghvi AT, et al. Patterns of hypothalamic-pituitary-go-nadal dysfunction in men with liver disease due to differing etiologies. Hepatology. 1981;1(1):39–46.
7. Bannister P, Oakes J, Sheridan P, Losowsky MS. Sex hormone changes in chronic liver disease: a matched study of alcoholic versus non-alcoholic liver disease. QJMed. 1987;63(240):305–13.
8. Sorrell JH, Brown JR. Sexual functioning in patients with end-stage liver disease before and after transplantation. Liver Transpl. 2006;12(10):1473–7.
9. Mandorfer M, et al. Beta blockers and chirrosis. Dig Liver Dis. 2017;49(1):3–10.
10. Piperno A, Rivolta MR, D'Alba R, Fargion S, Rovelli F, Ghezzi A, et al. Preclinical hypogonadism in genetic hemochromatosis in the early stage of the disease: evidence of hypothalamic dysfunction. J Endocrinol Investig. 1992;15(6):423–8.
11. Cundy TF, Butler J, Pope RM, Saggar-Malik AK, Wheeler MJ, Williams R. Amenorrhoea in women with non-alcoholic chronic liver disease. Gut. 1991;32(2):202–6.
12. Gavaler JS. Alcohol effects on hormone levels in normal postmenopausal women and in postmenopausal women with alcohol-induced cirrhosis. Recent Dev Alcohol. 1995;12:199–208.
13. Giard J-M, Terrault NA. Women with cirrhosis prevalence, natural history, and management. Gastroenterol Clin N Am. 2016;45(2):345–58.
14. Becker U. The influence of ethanol and liver disease on sex hormones and hepatic estrogen receptors in women. Dan Med Bull. 1993;40(4):447–59.
15. Cox TM, Kelly AL. Haemochromatosis: an inherited metal and toxicity syndrome. Curr Opin Genet Dev. 1998;8(3):274–81.
16. Leung PC, Steele GL. Intracellular signaling in the gonads. Endocr Rev. 1992;13(3):476–98.
17. Van Thiel DH. Ethanol: its adverse effects upon the hypothalamic-pituitary-gonadal axis. J Lab Clin Med. 1983;101(1):21–33.
18. Kourmanova A, et al. Reproductive dysfunctions in viral hepatitis. Gynecol Endocrinol. 2016;32(sup2):37–40.
19. Kim D, et al. Clinical Mol Hepatol. 2015;4(1):27–32.
20. Toda K, Miwa Y, Kuriyama S, Fukushima H, Shiraki M, Murakami N, et al. Erectile dysfunction in patients with chronic viral liver disease: its relevance to protein malnutrition. J Gastroenterol. 2005;40(9):894–900.
21. Schiavi RC, Schreiner-Engel P, White D, Mandeli J. The relationship between pituitary-gonadal function and sexual behavior in healthy aging men. Psychosom Med. 1991;53(4):363–74.
22. Keskin G, Gümüs AB, Orgun F. Quality of life, depression, and anxiety among hepatitis B patients. Gastroenterol Nurs. 2013;36(5):346–56.

23. Codes L, Asselah T, Cazals-Hatem D, Tubach F, Vidaud D, Paraná R, et al. Liver fibrosis in women with chronic hepatitis C: evidence for the negative role of the menopause and steatosis and the potential benefit of hormone replacement therapy. Gut. 2007;56(3):390–5.
24. Villa E, Karampatou A, Cammà C, Di Leo A, Luongo M, Ferrari A, et al. Early menopause is associated with lack of response to antiviral therapy in women with chronic hepatitis C. Gastroenterology. 2011;140(3):818–29.
25. Villa E, Vukotic R, Cammà C, Petta S, Di Leo A, Gitto S, et al. Reproductive status is associated with the severity of fibrosis in women with hepatitis C. PLoS One. 2012;7(9):e44624.
26. Karampatou A, et al. Premature ovarian senescence and a high miscarriage rate impair fertility in women with HCV. J Hepatol. 2017.
27. Hanson BM, Dorais JA. Reproductive considerations in the setting of chronic viral illness. Am J Obstet Gynecol. 2017;217(1):4–10.
28. Karaivazoglou K, Tsermpini EE, Assimakopoulos K, Triantos C. Sexual functioning in patients with chronic hepatitis C: a systematic review. Eur J Gastroenterol Hepatol. 2017;29(11):1197–205.
29. Laskus T, Radkowski M, Bednarska A, Wilkinson J, Adair D, Nowicki M, et al. Detection and analysis of hepatitis C virus sequences in cerebrospinal fluid. J Virol. 2002;76(19):10064–8.
30. Wilkinson J, Radkowski M, Laskus T. Hepatitis C virus neuroinvasion: identification of infected cells. J Virol. 2009;83(3):1312–9.
31. Soykan A, Boztaş H, İdilman R, Ozel ET, Tuzun AE, Ozden A, et al. Sexual dysfunctions in HCV patients and its correlations with psychological and biological variables. Int J Impot Res. 2005;17(2):175–9.
32. Dove LM, Rosen RC, Ramcharran D, Wahed AS, Belle SH, Brown RS, et al. Decline in male sexual desire, function, and satisfaction during and after antiviral therapy for chronic hepatitis C. Gastroenterology. 2009;137(3):873–84.
33. Elshimi E, Morad W, Mohamad NE, Shebl N, Waked I. Female sexual dysfunction among Egyptian patients with chronic hepatitis C. J Sex Med. 2014;11(3):768–75.
34. Danoff A, Khan O, Wan DW, Hurst L, Cohen D, Tenner CT, et al. Sexual dysfunction is highly prevalent among men with chronic hepatitis C virus infection and negatively impacts health-related quality of life. Am J Gastroenterol. 2006;101(6):1235–43.
35. Yang CC, Jiang X. Clinical autonomic neurophysiology and the male sexual response: an overview. J Sex Med. 2009;6(Suppl 3):221–8.
36. Kraus MR, Schäfer A, Bentink T, Scheurlen M, Weissbrich B, Al-Taie O, et al. Sexual dysfunction in males with chronic hepatitis C and antiviral therapy: interferon-induced functional androgen deficiency or depression? J Endocrinol. 2005;185(2):345–52.
37. Wellge BE, Sterneck M, Teufel A, et al. Pregnancy in primary sclerosing cholangitis. Gut. 2011;60(8):1117–21.
38. Gossard AA, Lindor KD. Pregnancyin a patient with primary sclerosing cholangitis. J Clin Gastroenterol. 2002;35(4):353–5.
39. Sun Y, Haapanen K, Li B, et al. Women and primary biliary cirrhosis. Clin Rev Allergy Immunol. 2015;48(2–3):285–300.
40. Lindor KD, Gershwin ME, Poupon R, et al. Primary biliary cirrhosis. Hepatology. 2009;50(1):291–308.
41. Kahramanoglu-Aksoy E, Yilmaz B, et al. Pregnancy in women with primary biliary cirrhosis. Autoimmun Rev. 2014;13(9):931–5.
42. Dyson JK, Wilkinson N, Jopson L, et al. The inter-relationship of symptom severity and quality of life in 2055 patients with primary biliary cholangitis. Aliment Pharmacol Ther. 2016;44(10):1039–50.
43. Thiele DL. Autoimmune hepatitis. Clin Liver Dis. 2005;9(4):635–46.
44. Krawitt EL. Autoimmune hepatitis. N Engl J Med. 2006;354(1):54–66.
45. Ferrarese A, Senzolo M, Burra P. Successful pregnancy in Alagille Syndrome. Dig Liver Dis. 2015;47(1):86–7.
46. Miller JC, Mastrobattista JM, Katz AR. Obstetrical and neonatal outcome in pregnancies after liver transplantation. Am J Perinatol. 2000;17(6):299–302.

47. Ross DS, Dollard SC, Victor M, et al. The epidemiology and prevention of congenital cytomegalovirus infection and disease: activities of the Centers for Disease Control and Prevention Workgroup. J Women's Health (Larchmt). 2006;15(3):224–9.
48. Laifer SA, Ehrlich GD, Huff DS, et al. Congenital cytomegalovirus infection in offspring of liver transplant recipients. Clin Infect Dis. 1995;20(1):52–5.
49. EASL. Clinical practice guidelines: management of hepatitis B virus infection. J Hepatol. 2017;67(2):370–98.
50. Holmgren C, Scott J. In: Saade GR, Foley MR, Phelan JP, et al., editors. Critical care obstetrics. Wiley; 2010.
51. Floreani A. Hepatitis C and pregnancy. World J Gastroenterol. 2013;19(40):6714–20.
52. Paternoster DM, Santarossa C, Grella P, et al. Viral load in HCV RNA positive pregnant women. Am J Gastroenterol. 2001;96(9):2751–4.
53. Pergam SA, Wang CC, Gardella CM, et al. Pregnancy complications associated with hepatitis C: data from 2003–2005 Washington state borth cohort. Am J Obstet Gynecol. 2008;199(1):38.e1–9.
54. Connell LE, Salihu HM, Salemi JL, et al. Maternal hepatitis B and hepatitis C carrier and perinatal outcome. Liver Int. 2011;31(8):1163–70.
55. Sato H, Tomita K, Yasue C, et al. Pregnant woman with non-comatose autoimmune acute liver failure in the second trimester rescued using medical therapy: a case report. Hepatol Res. 2014;45:1–7.
56. Candia L, Marquez J, Espinoza LR. Autoimmune hepatitis and pregnancy: a rheumatologist's dilemma. Semin Arthritis and Rheum. 2005;35:49–56.
57. Lohse AW, Mieli-Vergani G. Autoimmune hepatitis. J Hepatol. 2011;55:171–82.
58. Buchel E, Van Steenbergen W, Nevens F, et al. Improvement of autoimmune hepatitis during pregnancy followed by flare-up after delivery. Am J Gastroenterol. 2002;97:3160–5.
59. Heneghan MA, Norris SM, O'Grady JG, et al. Management and outcome of pregnancy in autoimmune hepatitis. Gut. 2001;48:97–102.
60. Schrumpf E, Boberg KM. Epidemiology of primary sclerosing cholangitis. Best Pract Res Clin Gastroenterol. 2001;15:553–62.
61. Berquist A, Montgomery SM, Lund U, et al. Perinatal events and the risk of developing primary sclerosing cholangitis. World J Gastroenterol. 2006;12:6037–40.
62. Floreani A, Caroli D, Lazzari R, et al. Intrahepatic cholestasis of pregnancy: new insights into its pathogenesis. J Matern Fetal Neonatal Med. 2013;26(14):1410–5.
63. Boregowda G, Shehata HA. Gastrointestinal and liver disease in pregnancy. Best Practice and Research. Clin Obstet Gynaecol. 2013;27:835–53.
64. Italian Association for the study of the Liver. AISF position paper on liver disease and pregnancy. Dig Liver Dis. 2016;48(8):860–8.
65. Fitzpatrick KE, Hinshaw K, Kurinczuk JJ, et al. Risk factors, management, and outcomes of hemolysis, elevated liver enzymes, and low platelets syndrome and elevated liver enzymes, low platelets syndrome. Obstet Gynecol. 2014;123(3):618–27.
66. Abildggard U, Hemidal K. Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP): a review. Eur J Obstet Gynecol Reprod Biol. 2013;166(2):117–23.
67. Bacq Y. Liver diseases unique to pregnancy: a 2010 update. Clin Res Hepatol Gastroenterol. 2011;35(3):182–93.
68. Aydin S, Ersan F, Ark C, et al. Partial HELLP syndrome: maternal, perinatal, subsequent pregnancy and long-term maternal outcomes. J Obstet Gynaecol Res. 2014;40(4):932–40.
69. Licata A, et al. Clinical course and management of acute and chronic viral hepatitis during pregnancy. J Viral Hepat. 2015;22(6):515–23.
70. Cho GJ, Kim YB, Kim SM, et al. Hepatitis A virus infection during pregnancy in Korea: hepatitis A infection on pregnant women. Obstet Gynecol Sci. 2013;56(6):368–74.
71. Pol S, Corouge M, Fontaine H. Hepatitis B virus infection and pregnancy. Clin Res Hepatol Gastroenterol. 2011;35(10):618–22.

72. Zhang S-L, Han X-B, Yue Y-F. Relationship between HBV viremia level of pregnant women and intrauterine infection: neated PCR for detection of HBV DNA. World J Gastroenterol. 1998;4(1):61–3.
73. Hay JE. Liver disease in pregnancy. Hepatology. 2008;47(3):1067–76.
74. Tosone G, Maraolo AE, Mascolo S, et al. Vertical hepatitis C virus transmission: main questions and answers. World J Hepatol. 2014;6(8):538–48.
75. Pembrey L, Newell ML, Tovo PA, et al. The management of HCV infected pregnant women and their children European paediatric HCV network. J Hepatol. 2005;43(3):515–25.
76. Abravanel F, Lhomme S, Dubois M, et al. Hepatitis E virus. Med Mal Infect. 2013;43(7):263–70.
77. Patra S, Kumar A, Trivedi SS, et al. Maternal and foetal outcomes in pregnant women with acute hepatitis E virus infection. Ann Intern Med. 2007;147(1):28–33.
78. Valla DC. The diagnosis and management of the Budd–Chiari syndrome: consensus and controversies. Hepatology. 2003;38(4):793–803.
79. James AH. Prevention and management of venous thromboembolism in pregnancy. Am J Med. 2007;120(10 Suppl 2):S26–34.
80. Grant WJ, McCashland T, Botha JF, et al. Acute Budd–Chiari syndrome during pregnancy: surgical treatment and orthotopic liver transplantation with successful completion of the pregnancy. Liver Transpl. 2003;9(9):976–9.
81. Rautou PE, Plessier A, Bernuau J, et al. Pregnancy: a risk factor for Budd–Chiari syndrome? Gut. 2009;58(4):606–8.
82. Barry JM. The evaluation and treatment of erectile dysfunction following organ transplantation. Semin Urol. 1994;12(2):147–53.
83. Lee S, Coco M, Greenstein SM, Schechner RS, Tellis VA, Glicklich DG. The effect of sirolimus on sex hormone levels of male renal transplant recipients. Clin Transpl. 2005;19(2):162–7.
84. Reinhardt W, Patschan D, Pietruck F, et al. Free androgen index is superior to total testosterone for short-term assessment of the gonadal axis after renal transplantation. Horm Res. 2005;64(5):248–52.
85. Liu L, Zhang J, Yuan J, et al. Characterization of a human regulatory subunit of protein phosphatase 3 gene (PPP3RL) expressed specifically in testis. Mol Biol Rep. 2005;32(1):41–5.
86. Carrera A, Moos J, Ning XP, et al. Regulation of protein tyrosine phosphorylation in human sperm by a calcium/calmodulin-dependent mechanism: identification of A kinase anchor proteins as major substrates for tyrosine phosphorylation. Dev Biol. 1996;180(1):284–96.
87. Fritsche L, Budde K, Dragun D, Einecke G, Diekmann F, Neumayer HH. Testosterone oncentrations and sirolimus in male renal transplant patients. Am J Transplant. 2004;4(1):130–1.
88. Kaczmarek I, Groetzner J, Adamidis I, Landwehr P, Mueller M, Vogeser M, et al. Sirolimus impairs gonadal function in heart transplant recipients. Am J Transplant. 2004;4(7):1084–8.
89. Tondolo V, Citterio F, Panocchia N, Nanni G, Favi E, Brescia A, Castagneto M. Gonadal function and immunosuppressive therapy after renal transplantation. Transplant Proc. 2005;37(4):1915–7.
90. Huyghe E, Zairi A, Nohra J, Kamar N, Plante P, Rostaing L. Gonadal impact of target of rapamycin inhibitors (sirolimus and everolimus) in male patients: an overview. Transpl Int. 2007;20(4):305–11.
91. Huyghe E, Kamar N, Wagner F, Yeung SJ, Apietto AH, El-Kahwaji L, et al. Erectile dysfunction in liver transplant patients. Am J Transplant. 2008;8(12):2580–9.
92. Seehofer D, Steinmueller T, Graef KJ, et al. Pituitary function test and endocrine status in patient with cirrhosis of the liver before and after hepatic transplantation. Ann Transplant. 2002;7(2):32–7.
93. Guichelaar MM, Malinchoc M, Sibonga J, Clarke BL, Hay JE. Immunosuppressive and postoperative effects of orthotopic liver transplantation on bone metabolism. Liver Transpl. 2004;10(5):638–47.
94. Frias J, Torres JM, Miranda MT, Ruiz E, Ortega E. Effects of acute alcohol intoxication on pituitary-gonadal axis hormones, pituitary-adrenal axis hormones, beta-endorphin and prolactin in human adults of both sexes. Alcohol Alcohol. 2002;37(2):169–73.

95. Madersbacher S, Ludvik G, Stulnig T, Grünberger T, Maier U. The impact of liver transplantation on endocrine status in men. Clin Endocrinol. 1996;44(4):461–6.
96. Aulakh BS, Singh SK, Khanna S, Kaura R, Goyal S. Impact of renal transplantation on gonadal function in male uremic patients-our experience. Transplant Proc. 2003; 35(1):316.
97. Compston JE. Osteoporosis after liver transplantation. Liver Transpl. 2003;9(4):321–30.
98. Tauchmanovà L, Carrano R, Sabbatini M, et al. Hypothalamic-pituitary-gonadal axis function after successful kidney transplantation in men and women. Hum Reprod. 2004;19(4): 867–73.
99. Mass K, Quint EH, Punch MR, Merion RM. Gynecological and reproductive function after liver transplantation. Transplantation. 1996;62(4):476–9.
100. Walcott WO, Derick DE, Jolley JJ, et al. Successful pregnancy in a liver transplant patient. Am J Obstet Gynecol. 1978;132(3):340–1.
101. Haagsma EB, Visser GH, Klompmaker IJ, et al. Successful pregnancy after orthotopic liver transplantation. Obstet Gynecol. 1989;74(3 Pt 2):442–3.
102. Christopher V, Al-Chalabi T, Richardson PD, et al. Pregnancy outcome after liver transplantation: a single-center experience of 71 pregnancies in 45 recipients. Liver Transpl. 2006;12(7):1138–43.
103. Scantlebury V, Gordon R, Tzakis A, et al. Childbearing after liver transplantation. Transplantation. 1990;49(2):317–21.
104. Jain AB, Reyes J, Marcos A, et al. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. Transplantation. 2003;76(5):827–32.
105. Jain A, Venkataramanan R, Fung JJ, et al. Pregnancy after liver transplantation under tacrolimus. Transplantation. 1997;64(4):559–65.
106. Patapis P, Irani S, Mirza DF, et al. Outcome of graftfunction and pregnancy following liver transplantation. Transplant Proc. 1997;29(1–2):1565–6.
107. Nagy S, Bush MC, Berkowitz R, et al. Pregnancy outcome in liver transplant recipients. Obstet Gynecol. 2003;102(1):121–8.
108. Wu A, Nashan B, Messner U, et al. Outcome of 22 successful pregnancies after liver transplantation. Clin Transpl. 1998;12(5):454–64.
109. Raakow R, Neuhaus R, Büscher U, et al. Parenthood following liver transplantation. Transplant Proc. 2001;33(1–2):1450–2.
110. Rupley DM, Janda AM, Kapeles SR, et al. Preconception counseling, fertility, and pregnancy complications after abdominal organ transplantation: a survey and cohort study of 532 recipients. Clin Transpl. 2014;28(9):937–45.
111. Kubo S, Uemoto S, Furukawa H, et al. Pregnancy outcomes after living donor liver transplantation: results from a Japanese survey. Liver Transpl. 2014;20(5):576–83.
112. Deshpande NA, Coscia LA, Gomez-Lobo V, et al. Pregnancy after solid organ transplantation: a guide for obstetric management. Rev Obstet Gynecol. 2013;6(3–4):116–25.
113. Burra P, Germani G, Masier A, De Martin E, Gambato M, Salonia A, Bo P, Vitale A, Cillo U, Russo FP, Senzolo M. Sexual dysfunction in chronic liver disease: is liver transplantation an effective cure? Transplantation. 2010;89(12):1425–9.
114. Terrault NA, Wright TL. Hepatitis C virus in the setting of transplantation. Semin Liver Dis. 1995;15(1):92–100.
115. De Bona M, Ponton P, Ermani M, et al. The impact of liver disease and medical complications on quality of life and psychological distress before and after liver transplantation. J Hepatol. 2000;33(4):609–15.
116. Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes of liver transplant recipients: a systematic review and meta-analysis. Liver Transpl. 2012;18(6):621–9.
117. Lessan-Pezeshki M, Ghazizadeh S, Khatami MR, et al. Fertility and contraceptive issues after kidney transplantation in women. Transplant Proc. 2004;36(5):1405–6.
118. Watnick S, Rueda J. Reproduction and contraception after kidney transplantation. Curr Opin Obstet Gynecol. 2008;20(3):308–12.

119. Zerner J, Doil KL, Drewry J, et al. Intrauterine contraceptive device failures in renal transplant patients. J Reprod Med. 1981;26(2):99–102.
120. Ortiz ME, Croxatto HB. Copper-T intrauterine device and levonorgestrel intrauterine system: biological bases of their mechanism of action. Contraception. 2007;75(6 Suppl):S16–30.
121. Fontenot HB, Harris AL. The latest advances in hormonal contraception. J Obstet Gynecol Neonatal Nurs. 2008;37(3):369–74.
122. Jabiry-Zieniewicz Z, Bobrowska K, Kaminski P, et al. Low-dose hormonal contraception after liver transplantation. Transplant Proc. 2007;39(5):1530–2.
123. Rayes N, Neuhaus R, David M, et al. Pregnancies following liver transplantation—how safe are they? A report of 19 cases under cyclosporine A and tacrolimus. Clin Transpl. 1998;12(5):396–400.
124. Coscia LA, Constantinescu S, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl. 2010:65–85.
125. Rodríguez-Castro KI, Gambato M, De Martin E, et al. Female gender in the setting of live transplantation. World J Tranplant. 2014;4(4):229–42.
126. Armenti VT, Daller JA, Constantinescu S, et al. Report from the National Transplantation Pregnancy Registry: outcomes of pregnancy after transplantation. Clin Transpl. 2006:57–70.
127. Women in Hepatology Group, Italian Association for the Study of the Liver (AISF). AISF position paper on liver transplantation and pregnancy. Dig Liv Dis. 2016;48:860–8.
128. Rabkin JM, de La Melena V, Orloff SL, et al. Late mortality after orthotopic liver transplantation. Am J Surg. 2001;181(5):475–9.
129. Coffin CS, Shaheen AAM, Burak KW, et al. Pregnancy outcomes among liver transplant recipients in the United States: a nationwide case-control analysis. Liver Transpl. 2010;16(1):56–63.
130. Jabiry-Zieniewicz Z, Dabrowski FA, Pietrzak B, et al. Pregnancy complications after liver transplantation. Int J Gynaecol Obstet. 2015;128(1):27–9.
131. Schreiber-Zamora J, Kociszewska-Najman B, Borek-Dziecioł B, et al. Neurological development of children born to liver transplant recipients. Transplant Proc. 2014;46(8):2798–801.
132. Keller F, Griesshammer M, Häussler U, et al. Pregnancy and renal failure: the case for application of dosage guidelines. Drugs. 2001;61(13):1901–20.
133. Beitins IZ, Bayard F, Ances IG, et al. The transplacental passage of prednisone and prednisolone in pregnancy near term. J Pediatr. 1972;81(5):936–45.
134. Carmichael SL, Shaw GM, Ma C, et al. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol. 2007;197(6):585.
135. Skuladottir H, Wilcox AJ, Ma C, et al. Corticosteroid use and risk of orofacial clefts. Birth Defects Res A Clin Mol Teratol. 2014;100(6):499–506.
136. Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. CMAJ. 2011;183(7):796–804.
137. Marushak A, Weber T, Bock J, et al. Pregnancy following kidney transplantation. Acta Obstet Gynecol Scand. 1986;65(6):557–9.
138. Davison JM, Lindheimer MD. Pregnancy in renal transplant recipients. J Reprod Med. 1982;27(10):613–21.
139. Cleary BJ, Källén B. Early pregnancy azathioprine use and pregnancy outcomes. Birth Defects Res A Clin Mol Teratol. 2009;85(7):647–54.
140. Loreno M, Bo P, Senzolo M, Cillo U, Noumov N, Burra P. Succesful pregnancy in a liver transplant recipient treated with lamivudine for de novo hepatitis B in the graft. Tranpl Int. 2005;17:730–4.
141. Hoeltzenbein M, Elefant E, Vial T, et al. Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services. Am J Med Genet A. 2012;158A(3):588–96.
142. Sifontis NM, Coscia LA, Constantinescu S, et al. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation. 2006;82(12):1698–702.

143. Information for Healthcare Professionals: Mycophenolate Mofetil (marketed as CellCept) and Mycophenolic Acid (marketed as Myfortic). United States Food and Drug Administration; 2013.
144. European best practice guidelines for renal transplantation Section IV: Longterm management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. Nephrol Dial Transplant. 2002;17(Suppl 4):50–5.
145. Jankowska I, Oldakowska-Jedynak U, Jabiry-Zieniewicz Z, et al. Absence of teratogenicity of sirolimus used during early pregnancy in a liver transplant recipient. Transplant Proc. 2004;36(10):3232–3.
146. Chu S-H, Liu K-L, Chiang Y-J, et al. Sirolimus used during pregnancy in a living related renal transplant recipient: a case report. Transplant Proc. 2008;40(7):2446–8.
147. Veroux M, Corona D, Veroux P. Pregnancy under everolimus-based immunosuppression. Transpl Int. 2011;24(12):e115–7.
148. Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics. 2012;129(3):e827–41.
149. Constantinescu S, Pai A, Coscia LA, Davison JM, Moritz MJ, Armenti VT. Breast-feeding after transplantation. Best Pract Res Clin Obstet Gynaecol. 2014;28(8):1163–73.