



## Reproductive health and pregnancy management in liver transplantation recipients

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Pregnancy in liver transplantation (LT) recipients has become an increasingly important topic in hepatology and obstetrics. Chronic liver disease, once predominantly affecting older individuals, is now more common among women of reproductive age due to rising prevalence of metabolic dysfunction-associated steatotic liver disease and alcohol-related liver disease. While cirrhosis can impact fertility through various mechanisms, many women retain or regain fertility with improved liver function. LT typically restores gonadal function, with 70%–95% of recipients experiencing menstrual normalization within a year. Pregnancy in LT recipients is considered high-risk, requiring careful management and multidisciplinary care. Most experts recommend waiting at least 1–2 years post-transplantation before conception to allow for graft stabilization and reduced immunosuppression. Pre-pregnancy management includes adjusting immunosuppressive agents, folic acid supplementation, cervical cancer screening, and appropriate vaccinations. Maternal complications in LT recipients include higher rates of pregnancy-induced hypertension, pre-eclampsia, and gestational diabetes compared to the general population. Fetal outcomes show higher rates of preterm birth and intrauterine growth restriction, though live birth rates have improved over time. The incidence of congenital abnormalities appears comparable to the general population. Postpartum management requires close monitoring of immunosuppressant levels and regular follow-ups. Breastfeeding is not absolutely contraindicated, but requires careful consideration of potential risks and benefits. This review summarizes current knowledge on fertility and pregnancy outcomes in these populations.

**Keywords:** Pregnancy; Liver transplantation; Contraception; Immunosuppressants

### INTRODUCTION

Pregnancy in patients with cirrhosis and liver transplantation (LT) recipients has become an increasingly important topic in hepatology and obstetrics. This shift is due to several factors that have changed the landscape of liver

disease management and reproductive medicine over the past few decades. Chronic liver disease, once predominantly affecting older individuals, is now more common among women of reproductive age [1]. This shift is largely attributed to the rising prevalence of metabolic dysfunction-associated steatotic liver diseases and alcohol-related

liver disease in younger populations.

Improvements in medical management of chronic liver diseases have led to better outcomes and longer survival rates. This means that more women with advanced liver disease are reaching and maintaining reproductive age [2]. Additionally, the success of LT has dramatically improved the quality of life and survival rates for patients with end-stage liver disease, allowing many to consider pregnancy post-transplantation [3]. The field of reproductive medicine has made significant strides, offering new possibilities for women with liver disease. Assisted reproductive technologies have enabled successful pregnancies in patients who were previously considered infertile. This includes in vitro fertilization techniques that have been successfully used in both patients with cirrhosis and LT recipients [4].

Despite these advancements, pregnancy in the context of cirrhosis or post-LT presents unique challenges. These pregnancies are considered high-risk due to potential complications for both the mother and the fetus. Issues such as graft rejection, medication adjustments, and increased risks of preterm birth and low birth weight (LBW) require careful management and multidisciplinary care [5]. Understanding the complexities of fertility, pregnancy outcomes, and optimal management strategies in these populations is crucial for providing the best care and counseling to these patients.

This review aims to summarize the current knowledge on fertility and pregnancy in patients with LT recipients, addressing key issues such as preconception counseling, timing of pregnancy, management of immunosuppression, and potential complications.

## REPRODUCTIVE HEALTH IN WOMEN WITH CHRONIC LIVER DISEASE

Peak fertility typically occurs between the ages of 15 and 44, and chronic liver disease is common among women, especially in their 30s and 40s [6]. Pregnancy in patients with cirrhosis was considered rare, primarily due to the assumption of widespread infertility in this population [7]. Infertility in these patients is thought to result from dysfunction of the hypothalamic-pituitary axis and impaired hepatic metabolism of sex hormones, leading to anovulation and amenorrhea [8].

Around 30%–50% of women with chronic liver disease experience amenorrhea [7]. Factors contributing to the development of amenorrhea include the underlying cause of liver disease, nutritional status, and metabolic or endocrine

dysfunction. Hypothalamic function and gonadotropin-releasing hormone (GnRH) secretion are affected by multiple factors. Malnutrition alone can lead to hypothalamic hypogonadotropic amenorrhea, and cirrhosis can also directly impair hypothalamic function [9]. Disruption of the hypothalamic-pituitary axis, combined with decreased hepatic metabolism of sex hormones, portosystemic shunting of weak androgens, and peripheral conversion of androgens, leads to hormonal imbalances [3]. In the early stages of liver disease, estrogen levels may be elevated, though some studies indicate low estradiol levels in more advanced liver diseases [7]. The incidence of alcohol-related liver disease is rising among women of childbearing age [10]. Alcohol can also affect the hypothalamic-pituitary axis and directly disrupt ovarian function, potentially resulting in primary gonadal failure characterized by low estradiol levels and suppressed GnRH release [11].

Pregnancy-related complications are more frequent in women with cirrhosis, with higher rates of maternal issues, such as antepartum hospitalization, cesarean deliveries, and severe complications like variceal bleeding [12]. Decompensated cirrhosis significantly raises risks, including hepatic decompensation, thromboembolism, and peripartum infections [13]. Fetal complications, including preterm birth and intrauterine growth restriction (IUGR), are also more common in patients with chronic liver disease [12]. To reduce these risks, providers should educate cirrhotic patients and use tools like the model for end-stage liver disease score to predict outcomes, with scores above 10 (83% sensitivity, 83% specificity) showing a strong correlation with gestational hepatic decompensation [14].

However, recent research suggests that fertility issues in cirrhosis may have been overestimated [15]. While cirrhosis can impact fertility through various mechanisms, many women with cirrhosis retain their fertility or experience its restoration with improved liver function. In addition, this increase is due to greater patient awareness, rising demand, advancements in clinical care, pre-pregnancy counseling, and assisted reproductive techniques. Enhancing fertility in women with chronic liver disease should involve optimizing liver synthetic function and maintaining overall liver health.

## FERTILITY AFTER LIVER TRANSPLANTATION

LT recovers gonadal function in women with end-stage liver disease and increases the likelihood of pregnancy. Following successful LT, menstruation can resume as early

as the first month with 70%–95% of recipients experiencing normalization within a year [16]. This suggests that fertility is restored within 6–12 months due to the rebalancing of sex hormones and reversal of altered pituitary feedback mechanisms. Previous studies have shown varied changes in levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol, and progesterone before and after LT. A systematic review, which included only four studies out of 12 focusing on women, found that estradiol and prolactin levels are elevated before LT and decrease post-transplantation, while FSH and LH levels tend to rise after LT [16].

However, some recipient individuals experience anovulation. Persistent anovulation in female LT recipients may result from an imbalance between progesterone and estrogen, with relative hyperestrogenism increasing the risk of gynecological issues, such as uterine bleeding due to endometrial hyperplasia [3]. Progesterone has been shown to help reduce vaginal bleeding in LT recipients [17]. LT positively influences several aspects of sexual function; however, it has limited effectiveness in fully resolving pre-transplantation sexual dysfunction. Sexual dysfunction post-LT is multifaceted, influenced by age, social factors, medication side effects, and changes in sexual desire [18]. Although, many of these issues improve after LT, some patients continue to face challenges. One study found that female recipients with unresolved sexual dysfunction often struggled with self-worth, influenced by unemployment, ongoing health concerns, changes in body image, and depression [19].

## PREGNANCY SCHEDULE

The timing of pregnancy after LT is a critical consideration for patients and healthcare providers. Most experts recommend a waiting period of at least 1 to 2 years post-transplantation before attempting conception. This delay allows for several important factors to stabilize; achieving stable graft function, allowing for complete post-operative recovery, reducing immunosuppression levels, and lowering the risks of opportunistic infections and acute cellular rejection (ACR) during this stage of recovery.

The National Transplantation Pregnancy Registry, a US-based registry using questionnaires to study pregnancy outcomes in solid organ transplantation recipients, reported that waiting over 2 years post-transplantation before conception was associated with lower rates of LBW, rejection, and graft loss [20]. Conversely, women who conceived

within 6 months post-LT faced the highest risk for these complications. Additionally, a single-center study reported only one successful live birth among seven pregnancies conceived within a year of LT, prompting the authors to advise delaying conception for a minimum of 2 years post-transplantation [21]. Another single-center study of 71 pregnancies found no significant difference in live birth rates (LBRs) between pregnancies conceived within the first year post-LT and those conceived after 1 year. However, the study noted higher rates of prematurity, LBW, and ACR among pregnancies in the early group, supporting the recommendation to wait at least 1 year before conception [22].

Patients at higher risk—such as those with recent ACR, unstable graft function, or graft failure—are more likely to experience adverse pregnancy outcomes. In these cases, it is advisable to delay pregnancy and to observe a stabilization period, typically 3 to 6 months prior to conception. Pre-pregnancy counseling and consultation with a medical obstetrician, along with a multidisciplinary approach, are also recommended during this preparation phase.

## CONTRACEPTION IN LIVER TRANSPLANTATION RECIPIENTS

The rapid return of fertility necessitates early counseling regarding contraception and family planning. Effective contraception is crucial in the early post-transplantation period when pregnancy should be avoided. All women scheduled to begin mycophenolate mofetil (MMF) must receive contraceptive counseling and have a negative pregnancy test before beginning treatment. Ideally, patients should use two forms of contraception for at least 4 weeks prior to initiating MMF, throughout the treatment period, and for 12 weeks after stopping the medication [3]. The optimal contraceptive method that is safe, effective, and reversible for female LT recipients remains unclear. For those who have completed their family, female sterilization or partner vasectomy may be appropriate considerations.

Intrauterine devices (IUDs) are generally considered safe and effective in LT recipients. However, IUDs may be less effective in immunosuppressed patients due to reduced local anti-inflammatory effects in the uterus. In a case series involving kidney transplantation (KT) recipients, three out of five patients reported unplanned pregnancies [23]. Although the American Society of Transplantation does not recommend IUDs as a first-choice contraceptive method in transplantation recipients, this remains controversial, as

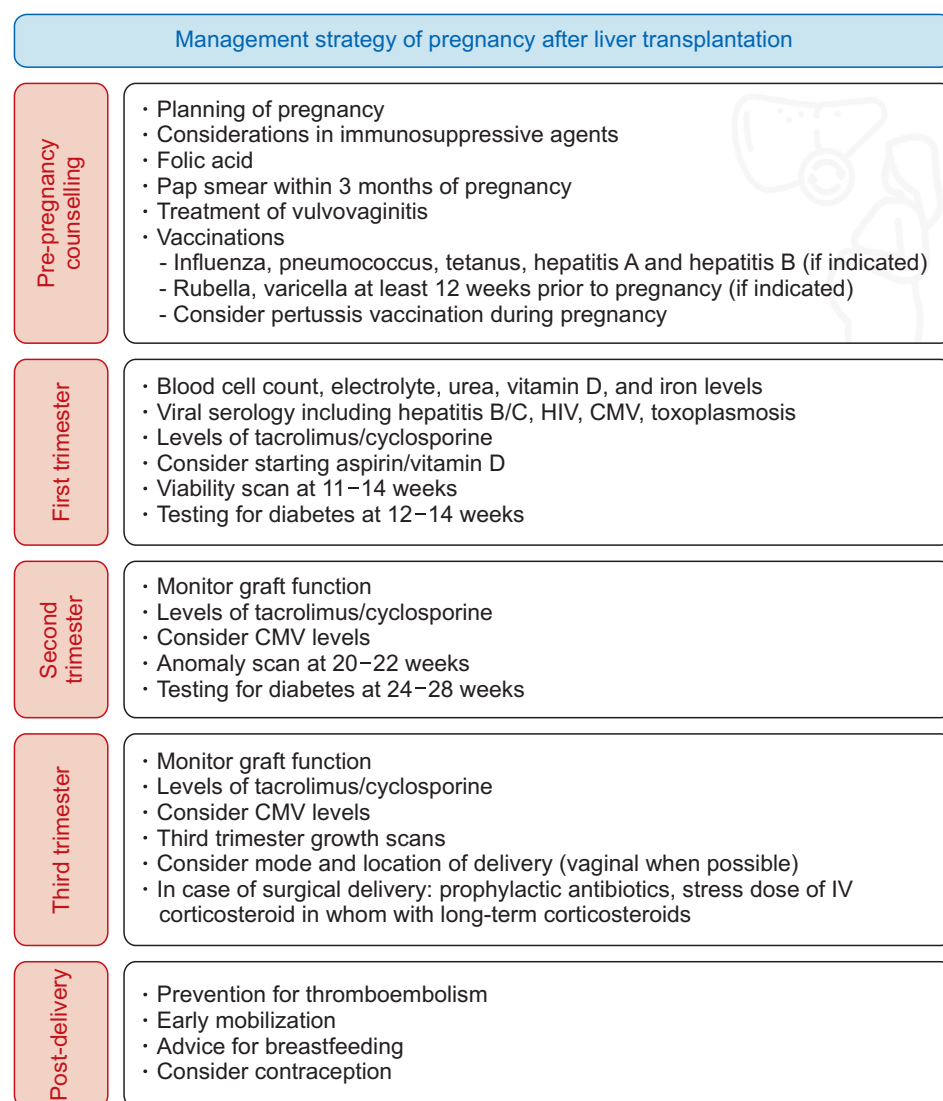
IUDs can be an effective option for many women. Further research is needed to evaluate their efficacy in post-transplantation patients.

Combined hormonal contraceptives should be used cautiously due to potential interactions with immunosuppressants and an increased risk of thrombosis. A systematic review on contraception use among KT and LT recipients showed no unplanned pregnancies or significant biochemical abnormalities in patients using low-dose oral or transdermal hormonal therapies [23]. However, two patients discontinued use due to thrombophlebitis and graft dysfunction, and some required changes to antihypertensive treatment. Additionally, a retrospective study of 15 patients using combined oral contraceptives or a transdermal patch found no clinical or biochemical issues, maintaining 100%

contraceptive efficacy [24]. Barrier methods are safe but have higher failure rates in LT recipients.

## PRE-PREGNANCY MANAGEMENT

LT recipients require careful pre-pregnancy management to ensure optimal outcomes for both mother and fetus. Planning for pregnancy in this patient population involves a multidisciplinary approach, including close collaboration between transplantation specialists, obstetricians, and infectious disease experts [25]. The management strategy should be tailored to each individual patient's needs and circumstances, taking into account the time since transplantation, graft function, and overall health status. Fig. 1 summarizes the preparation for pregnancy and manage-



**Fig. 1.** Preparation for pregnancy and management of liver transplantation recipients during pregnancy.

ment of LT recipients during pregnancy.

A primary consideration in pre-pregnancy management for LT recipients is the adjustment of immunosuppressive agents. These medications are crucial for preventing graft rejection but may pose risks to fetal development. MMF, in particular, is associated with an increased risk of congenital malformations and should be discontinued at least 6 weeks prior to conception [3]. Alternative immunosuppressive regimens, typically including tacrolimus, cyclosporine, azathioprine, or prednisone, which are considered relatively safe during pregnancy, should be established well before conception [25]. The transition to a pregnancy-compatible

immunosuppressive regimen should be carefully monitored to ensure continued graft stability. Effects of immunosuppressive drugs commonly used in LT recipients on pregnancy is provided in Table 1.

Folic acid supplementation is an essential component of pre-pregnancy care for all women, including LT recipients. To reduce the risk of neural tube defects, it is recommended that women begin taking 400–800 mg of folic acid daily before conception and continue throughout pregnancy [26]. This supplementation is particularly important in transplantation recipients, as they may have nutritional deficiencies due to their underlying condition or medication regimens.

**Table 1.** Summary of immunosuppressive drugs used in liver transplantation recipients on pregnancy

| Drug name                         | FDA category for pregnancy | Risk in mother                                                                                                                          | Risk in fetus                                                                                                                | Breastfeeding safety |
|-----------------------------------|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Tacrolimus                        | Category C                 | Hypertension<br>Gestational diabetes<br>Neurotoxicity<br>Renal dysfunction                                                              | Prematurity<br>Congenital anomalies<br>LBW<br>IUGR<br>Transient renal insufficiency                                          | Requires caution     |
| Corticosteroids                   | Category C                 | Hypertension<br>Gestational diabetes<br>Adrenal insufficiency<br>Osteonecrosis<br>Weight gain<br>Dyslipidemia<br>Infection<br>Dizziness | Teratogenic effects<br>Cleft palate<br>Premature rupture of membranes<br>Adrenal insufficiency<br>IUGR<br>LBW                | Use lowest dose      |
| Azathioprine                      | Category D                 | Leucopenia<br>Thrombocytopenia<br>Gastrointestinal trouble<br>Infection                                                                 | Congenital anomalies<br>Preterm delivery<br>LBW<br>IUGR<br>Thymic hypoplasia (usually normalizes within a year)              | No                   |
| Cyclosporine                      | Category C                 | Hypertension<br>Gestational diabetes<br>Pre-eclampsia<br>Renal dysfunction                                                              | Malformations<br>LBW<br>Skeletal retardation                                                                                 | No                   |
| mTOR inhibitors                   | Category C                 | Gastrointestinal trouble<br>Mucositis<br>Infection                                                                                      | Only animal studies- reduced fetal weight<br>Delayed ossification of skeletal structures                                     | No                   |
| OKT3 (murine monoclonal antibody) | Category C                 | Flu-like symptoms allergic reaction                                                                                                     | Unknown                                                                                                                      | Unknown              |
| Mycophenolate mofetil             | Category D                 | Leucopenia<br>Gastrointestinal trouble                                                                                                  | Malformation (22%, wide spectrum affecting cleft palate, ears, limbs, heart, esophagus, and kidneys)<br>Spontaneous abortion | No                   |

FDA, U.S. Food and Drug Administration; LBW, low birth weight; IUGR, intrauterine growth restriction; mTOR, mammalian target of rapamycin.

Cervical cancer screening is another crucial aspect of pre-pregnancy care. LT recipients should undergo a Pap smear within three months of planned pregnancy [25]. This screening is especially important in this population due to their increased risk of human papillomavirus infection and cervical dysplasia associated with long-term immunosuppression [27]. Any abnormalities detected should be addressed prior to conception to minimize potential complications during pregnancy. The treatment of vulvovaginitis, if present, is an important step in pre-pregnancy management. Vaginal infections can lead to complications during pregnancy, including preterm labor and premature rupture of membranes [28]. Therefore, any existing vulvovaginitis should be thoroughly evaluated and treated before conception is attempted.

Vaccinations are crucial in pre-pregnancy care for LT recipients due to their increased infection risk from immunosuppression. The vaccination strategy should be carefully planned considering the patient's immune status and timing of pregnancy. Inactivated vaccines (influenza, pneumococcus, tetanus, hepatitis A and B) can generally be safely administered to LT recipients and should be given well before pregnancy to ensure adequate antibody response [3]. Live vaccines (rubella, varicella) pose challenges in LT recipients. While typically contraindicated in immunosuppressed individuals, they may be considered in select cases if benefits outweigh risks. If deemed necessary and safe, these should be administered at least 12 weeks before conception. The decision should be made case-by-case, considering immunosuppression levels and disease exposure risk [25]. Pertussis vaccination is important for LT recipients during pregnancy. The Advisory Committee on Immunization Practices recommends Tdap vaccination for all pregnant women, preferably between 27–36 weeks gestation [29]. This protects both mother and fetus through passive antibody transfer. Due to immunosuppression, vaccine response may be suboptimal in LT recipients. Post-vaccination antibody titers should be checked, and additional booster doses may be necessary to achieve protective levels.

A comprehensive pre-pregnancy evaluation should include assessment of graft function, screening for chronic viral infections (such as cytomegalovirus and Epstein-Barr virus), evaluation of renal function, and optimization of any comorbid conditions such as hypertension or diabetes [30]. Medications should be reviewed and adjusted as necessary, with potentially teratogenic drugs being replaced with safer alternatives whenever possible.

## OUTCOMES OF PREGNANCY IN LIVER TRANSPLANTATION RECIPIENTS

### Maternal Outcomes

Pregnancy-related hypertension (PIH), pre-eclampsia, preterm birth, and IUGR are significant concerns for LT recipients [31]. Maternal mortality rates in LT recipients are comparable to the general population, with death rates ranging from 0%–1% [32,33]. Additionally, high-risk recipients with post-transplantation complications may face poorer outcomes, making it crucial to delay conception and closely monitor these patients.

Studies have shown higher rates of PIH in LT recipients compared to controls (16%–30% vs. 9%) [32,34]. Pre-eclampsia is a primary cause of preterm delivery in LT recipients, with reported rates between 7%–12%, which have decreased over time due to improved management of immunosuppression and pre-eclampsia-related risk factors [35–38]. The reported graft rejection rates in pregnant LT recipients vary widely, from 0%–20% while postpartum rejection rates range from 3%–12% [21,22,32,39–41]. Graft loss during pregnancy due to ACR is rare, but some cases of graft loss post-delivery due to recurrent autoimmune hepatitis and chronic rejection have been reported [40]. If graft dysfunction is suspected during pregnancy, liver biopsy and appropriate assessment should be conducted [42]. For patients with ACR during pregnancy, corticosteroid therapy or adjustments in immunosuppressive therapy are generally effective [22,40,41].

The rate of gestational diabetes (GD) among LT recipients ranges from 0%–11% [22,33,34]. A North American population-based study found GD rates were significantly higher in LT recipients than in the general population (8.6% vs. 5.4%) [33]. Rates of antepartum hemorrhage are similar between LT recipients and the general population, but postpartum hemorrhage is significantly more common in LT recipients (8% vs. 3%) [32].

Infection rates during pregnancy are comparable between LT recipients and the general population, though urinary infections are more frequent in LT recipients than non-LT recipients (5.3% vs. 1.4%) [32,33,43]. Consequently, pregnant LT recipients are considered high-risk and should be managed by a multidisciplinary team including an experienced obstetrician and transplantation physician, with vigilant screening and management for maternal complications.

### Fetal Outcomes

The LBR among pregnancies in LT recipients is approximately 65% and has improved over time due to better care for high-risk patients and fewer unplanned pregnancies [22,41,44]. Spontaneous abortion rates in LT recipients range from 11%–19%, though exact rates are challenging to determine due to inconsistent reporting [21,22,41]. Still-birth rates are generally low, between 0%–1.2%, though some studies have reported rates as high as 12% [21,36,45].

Preterm births are common in LT recipients, with rates reported between 14%–53% [22,41,44]. One study found a 39% preterm birth rate in LT recipients, significantly higher than the general U.S. population rate of 14% [34]. This elevated rate is likely due to the higher incidence of pregnancy-related complications in LT recipients.

A meta-analysis found that the average birth weight in LT recipients (2,866 g) was significantly higher than in KT recipients (2,420 g), although lower than the general U.S. population (3,298 g) [34]. Rates of IUGR in LT recipients vary from 5%–20%, with some studies indicating that IUGR is statistically more common in LT recipients compared to the general population [45–47].

Recurrent CMV infection in immunosuppressed female patients can lead to congenital CMV infection, which, if untreated, may cause severe fetal complications such as hydrops fetalis, stillbirth, mental retardation, visual or hearing loss, prematurity, or death [48,49]. Regular CMV monitoring during pregnancy in LT recipients is therefore necessary.

The incidence of congenital abnormalities in children of LT recipients is reported to be low, ranging from 0%–4% [20,32,40,50]. Reported abnormalities include tracheo-esophageal fistula, pyloric stenosis, ventricular septal defects, and tetralogy of Fallot; however, no consistent pattern of malformation has been observed. There is no definitive evidence that the rate of congenital abnormalities differs between LT recipients and the general population.

### POSTPARTUM MANAGEMENT IN LIVER TRANSPLANTATION RECIPIENTS

Fluid retention for several weeks followed by normalization after delivery can alter immunosuppressant levels in LT recipients. Consequently, repeated testing of immunosuppressant levels is necessary within the first month postpartum [3]. Female LT recipients should also attend regular follow-up visits during the initial 3 months after delivery.

International guidelines suggest that breastfeeding need not be absolutely contraindicated in LT recipients [51]. Pa-

tients should be offered a discussion about the potential risks of drug exposure alongside the benefits of breastfeeding [52]. Prednisolone doses up to 20 mg/day are generally considered safe for infants [53]. Although breastfeeding on cyclosporine is not contraindicated in clinical practice, the American Academy of Pediatrics advises against it due to concerns about potential immunosuppression in the infant [54]. Limited data are available on the safety of MMF and mTOR inhibitors during breastfeeding. Therefore, additional studies are needed to establish definitive guidelines.

### CONCLUSIONS

Pregnancy in LT recipients is expected to rise in frequency and presents unique medical challenges that require careful management and multidisciplinary care.

While fertility may be impaired in cirrhotic patients, LT often restores reproductive function, creating new possibilities for family planning. Despite higher rates of maternal and fetal complications, overall pregnancy outcomes in LT recipients have improved over time, largely due to advancements in clinical care and increased awareness of the specific needs of this patient population. Future research should focus on optimizing immunosuppression strategies during pregnancy, further elucidating the long-term outcomes for children born to LT recipients, and developing more tailored guidelines for contraception and breastfeeding in this unique patient group.

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### CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

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Conceptualization: HAL. Data curation: HAL. Investigation: HAL. Methodology: HAL. Resources: HAL. Supervision: HAL. Visualization: HAL. Writing – original draft: HAL.

Writing – review & editing: HAL.

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