# Pregnancy After Liver Transplantation: Outcomes From a Single-Center Experience

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***Background/Objectives:*** **Although much has been learnt regarding pregnancy after liver transplantation, data from India are scant. Hence, we evaluated the maternal and fetal outcomes of pregnancies after liver transplantation at our center.** ***Methods:*** **We conducted a retrospective review of all patients who underwent liver transplantation and later conceived at our center between 2006 and 2019.** ***Results:*** **Of the 750 liver transplantations performed at our center, 129 were female and 62 of them were in the childbearing age group (15–44 years). A total of seven conceptions occurred in seven patients during the study period. All the pregnancies occurred spontaneously. The median age of the patients at the time of liver transplantation and conception was 25 years (range, 24–33 years) and 29 years (range, 26–36 years), respectively. The median interval between transplantation and conception was 40 months (range, 7–48 months). All patients were on tacrolimus monotherapy. None of the patients had rejection during pregnancy despite a low median tacrolimus trough level of 2.7 ng/mL. Live birth (five cesarean and one normal) occurred in six of seven pregnancies at a median gestation age of 37.5 weeks. Mean birth weight was 3055.8 g (range, 2470–3635 g). Antenatal rubella infection and grade III intrauterine growth restriction resulting in still birth at 29 weeks occurred in one patient. The median postnatal follow-up was 25 months (range, 2–81 months). All babies and mothers were healthy.** ***Conclusions:*** **Pregnancy after liver transplantation has a favorable outcome with a multidisciplinary team approach. There is a physiological reduction of tacrolimus trough levels during pregnancy for which dose augmentation is not usually required.** **(J Clin Exp Hepatol 2020;10:329–333)**

Liver Transplantation

Females of childbearing age constitute a significant percentage of patients undergoing liver transplantation for end-stage liver failure due to acute or chronic etiologies. Primary and secondary infertility often occurs in chronic liver disease. After transplantation, fertility is restored in many women and pregnancy becomes a reality.[1] Tacrolimus, a potent and widely used immunosuppressant, is known to exhibit complex pharmacokinetic behavior in pregnancy because of the physiological changes occurring at that time.[2] The management of immunosuppression in pregnancy is challenging, requiring vigilant assessment of the balance between the risk of rejection and adverse events for mother and/or fetus. Pregnancy after liver transplantation has a higher risk of pre-eclampsia, gestational diabetes, spontaneous abortion, preterm labor, and fetal growth restriction.[3] However, increasing experience and data with the management of these patients have enabled minimization of risks. Although much has been learnt regarding pregnancy after liver transplantation based on data from the United States, Europe and Japan,[4–8] data from India are scant. Here, we report the maternal and fetal outcomes of pregnancies after liver transplantation at our center.

## PATIENTS AND METHODS

We conducted a retrospective review of all patients who underwent liver transplantation at our center between 2006 and 2019. Of the 750 liver transplantations performed at our center, 129 were female and 62 of them were in the childbearing age group (range, 15–44 years). Among these, the patients who conceived and received prenatal care at our center were included for analysis (n = 7). This study was conducted in accordance with the principles that have their origin in the Declaration of Helsinki.

The medical and electronic records of the patients were reviewed and demographic data were collected in standard data collection form. Details regarding the immunosuppressive therapy inclusive of whole blood tacrolimus trough levels at conception, during pregnancy, at delivery and postpartum were obtained. Maternal complications including vaginal bleeding, infection, hypertension, pre-eclampsia, gestational diabetes, graft rejection, and graft

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*Abbreviations:* ALT: alanine aminotransferase; AST: aspartate aminotransferase; IgG: immunoglobulin G; IUD: intrauterine death; IUGR: intrauterine growth restriction; US FDA: United States Food and Drug Administration
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**Table 1 Details of Pregnancy, Maternal and Fetal Outcomes in Liver Transplant Recipients.**

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|---|---|---|---|---|---|---|---|
| Indication for transplantation | Seronegative ALF | Wilson's disease | Hepatitis B induced ALF | Noncirrhotic portal fibrosis (acute on CLF) | Seronegative ALF | Seronegative ALF | Autoimmune liver disease (acute on CLF) |
| Type of transplant | LDLT | DDLT | LDLT | LDLT | LDLT | LDLT | LDLT |
| Age at transplantation (years) | 25 | 33 | 28 | 25 | 25 | 24 | 27 |
| Age at conception (years) | 28 | 36 | 32 | 26 | 29 | 28 | 30 |
| Interval between transplantation and conception (months) | 30 | 42 | 40 | 7 | 48 | 42 | 39 |
| Parity | G3P2L2 | G4P1L1A2 | G2P1L1 | G2P1L1 | G3P2L1 | G3P1L1A1 | Primigravida |
| Way of conception | Spontaneous | Spontaneous | Spontaneous | Spontaneous | Spontaneous | Spontaneous | Spontaneous |
| Mode of delivery | Cesarean (emergency) | Vaginal (vacuum assisted) | Cesarean (emergency) | Cesarean (elective) | Cesarean (emergency) | Cesarean (emergency) | Vaginal (induced IUD expulsion) |
| Indication for delivery mode | Oblique lie, fetal distress | Failure of maternal power | Failed TOLAC, grade II meconium | Previous cesarean | Previous cesarean in labor | Non progression of labor | Stage III IUGR and IUD |
| Gestation age (weeks) | 38 | 38 | 37 | 38 | 37 | 37 | 29 |
| Birth weight (g) | 2850 | 3380 | 2980 | 2470 | 3635 | 3020 | 400 |
| Maternal complications | Chicken pox | No | No | No | No | No | Rubella |
| Fetal outcomes (Live/Still birth) | Live | Live | Live | Live | Live | Live | Still |
| Outcome of recipient (length of follow-up after delivery, months) | Alive (81) | Alive (76) | Alive (41) | Alive (13) | Alive (2) | Alive (25)[a] | Alive (10) |

ALF, Acute liver failure; CLF, Chronic liver failure; DDLT, Deceased donor liver transplantation; IUD, Intrauterine death; IUGR, Intrauterine growth restriction; LDLT, Living donor liver transplantation; TOLAC, Trial of labor after cesarean.
[a]Lost to follow-up.

loss were recorded. Details regarding obstetric complications (preterm labor, premature rupture of membrane, and placenta previa), pregnancy losses (elective and spontaneous termination of pregnancy), gestational duration, mode of delivery, live birth rate, birth weight, fetal growth retardation, and congenital abnormalities were also recorded. Long-term follow-up data on mother and infant were obtained.

Data analysis was performed using SPSS 20 software.

## RESULTS

A total of seven pregnancies in seven patients was identified during the study period. Among these, six patients received living donor liver grafts whereas one had deceased donor liver transplant. All the pregnancies occurred spontaneously. The details of seven patients are depicted in Table 1. The median age of the patients at the time of liver transplantation and conception was 25 years (range, 24–33 years) and 29 years (range, 26–36 years), respectively. The

**Table 2 Details of Immunosuppression.**

| | At conception | | During pregnancy | | At delivery | | Postpartum (at least 2 months after delivery) | |
|---|---|---|---|---|---|---|---|---|
| | TAC level (ng/mL) | TAC dose (mg/day) | TAC level (ng/mL) | TAC dose[a] (mg/day) | TAC level (ng/mL) | TAC dose (mg/day) | TAC level (ng/mL) | TAC dose (mg/day) |
| Patient 1 | 3.1 | 2 | 1.1 | 2 | 1.9 | 2.5 | 4.8 | 2.5 |
| Patient 2 | NA | 2 | 1.4 | 5 | 1.9 | 6 | 4.3 | 5 |
| Patient 3 | 3.4 | 4 | 2.7 | 4 | 2.8 | 4 | 2.4 | 5 |
| Patient 4 | 6.5 | 3 | 7.1 | 4 | 5.1 | 4 | 7.1 | 3 |
| Patient 5 | 4.6 | 3 | 3.0 | 3 | 4.2 | 3 | 5.4 | 3 |
| Patient 6 | 5.5 | 4 | 0.5 | 4 | 1.7 | 4 | 6.2 | 4 |
| Patient 7 | 8.2 | 4 | 4.1 | 4 | 3.4 | 4 | 5.5 | 4 |

NA, Not available; TAC, tacrolimus.
[a]The maximum dose received at any time point during pregnancy. The tacrolimus levels are whole blood trough levels.

median interval between transplantation and conception was 40 months (range, 7–48 months).

All the patients were on tacrolimus monotherapy at the time of conception. Details of tacrolimus dose and trough levels are given in Table 2. The median dose of tacrolimus at the time of conception was 3 mg/day (range, 2–4 mg/day). The median tacrolimus trough level at conception was 5.1 ng/mL (range, 3.1–8.2 ng/mL). All patients received tacrolimus throughout pregnancy [median dose 4 mg/day (range, 2–5 mg/day); median tacrolimus trough level: 2.7 ng/mL (range, 0.5–7.1 ng/mL)]. At the time of delivery, the median dose and trough levels of tacrolimus were 4 mg/day (range, 2.5–6 mg/day) and 2.8 ng/mL (range, 1.7–5.1 ng/mL), respectively. In most patients after delivery, the trough level of tacrolimus increased without changing the tacrolimus dose. Indeed in two patients, this occurred despite decrease in tacrolimus dosage. In three patients (patient 1, 2, and 4), the dose of tacrolimus was modified during pregnancy. Patient 1 developed chicken pox at 18 weeks of gestation and received acyclovir along with dose reduction of tacrolimus. In patient 2, the trough tacrolimus level was 1.4 at three months of gestation. Her liver function tests were normal. Nevertheless, we increased the dose (to a maximum of 5 mg/day during pregnancy) because of low whole blood tacrolimus levels despite which the trough level remained at 1.9 at the time of delivery. In patient 4, tacrolimus dose was increased to 4 mg/day because of mild elevation in liver enzymes (aspartate aminotransferase, 44.8 IU/L and alanine aminotransferase, 89.6 IU/L), after which transaminases normalized. No patient had liver biopsy during pregnancy. Patient 3 was a case of hepatitis B and was on entecavir at the time of conception, which was switched over to tenofovir.

In the present study, six pregnancies (85.7%) ended in live birth. Pregnancy of patient 7, initially transplanted for autoimmune liver disease was complicated by grade III intrauterine growth restriction (IUGR). This patient's 22-week Doppler showed growth restriction of fetus with reduced liquor around it. The abnormal Doppler suggested an extrinsic cause for the IUGR. Nevertheless, in view of the early onset symmetrical IUGR, a coexisting intrinsic fetal cause (like chromosomal anomaly, fetal infection or single gene disorder) and dysfunction of the fetal side of the placenta could not be ruled out completely. A maternal TORCH screening suggested rubella infection (rubella IgG antibody, 17.5 IU/mL). Fetal Doppler at 27 weeks of gestation showed stage III IUGR with all the growth parameters falling below the first percentile for the period of gestation. In her 29th week, intrauterine death was detected and she was induced with mifepristone and misoprostol.

Acute rejection occurred in none of the patients. There were no maternal deaths. Details of live births, gestational age, type of delivery, birth weight, and maternal and fetal complications are given in Table 1.

## DISCUSSION

In this single-center experience, we have demonstrated that in majority of patients, pregnancy after liver transplantation can have favorable outcomes for the mother, fetus, and allograft.

There is still a lack of consensus regarding the optimal time of conception after liver transplantation, with most guidelines recommending a wait period of one to two years after transplantation. After this interval, the immunosuppressive therapy is usually at maintenance levels and the risk of rejection and infections is lower.[9,10] Reports have confirmed that the longer the interval between transplantation and conception, the lesser the risk of pregnancy complications.[7,11] In our series, only one patient (patient 4) conceived before one year of transplantation. Nonetheless, this patient had no complications during pregnancy and delivered a healthy baby at 38 weeks of gestation.

The management of immunosuppression in pregnancy is challenging, requiring vigilant assessment of the balance between the risk of rejection and adverse events for mother and/or fetus. Tacrolimus, classified as US Food and Drug Administration (FDA) pregnancy category C medication,[12] is a potent and widely used immunosuppressive drug in liver transplant recipients.[13] Pregnancy in tacrolimus-treated transplant recipients has been reported to result in favorable outcomes.[14,15] Mycophenolate is not recommended during pregnancy (US FDA pregnancy category D). In case an antimetabolite is required during pregnancy, azathioprine can be preferred.[16] In our study, all patients were on tacrolimus monotherapy at the time of conception (dose: 2–4 mg/day and trough level: 3.1–8.3 ng/mL). Patient 3, a case of hepatitis B was on entecavir (US FDA pregnancy category C)[17] at the time of conception which was switched over to tenofovir (US FDA pregnancy category B).[18]

All patients received tacrolimus during pregnancy. However, during pregnancy, the whole-blood tacrolimus trough levels were found to be reduced (median 2.7 ng/mL). There may be several reasons for the reduced trough levels of tacrolimus observed during pregnancy. Tacrolimus binds strongly to both erythrocytes and plasma proteins (approximately 99%) and is a substrate for cytochrome P-450 system (CYP3A) and P-glycoprotein. The increase in plasma volume and subsequent hemodilution during pregnancy can decrease the serum protein (albumin, alpha-1 acid glycoprotein) concentrations which can result in increased unbound fraction of tacrolimus (clinically active form of the drug). However, owing to increased CYP3A activity during pregnancy, there is rapid clearance of tacrolimus from blood and lower blood trough levels. In addition, increased P-glycoprotein expression during pregnancy can enhance the intestinal efflux of tacrolimus resulting in its decreased intestinal absorption and bioavailability.[2,12] Because tacrolimus is a drug with a narrow therapeutic range, clinicians usually adjust doses based on tacrolimus trough level in whole blood which can lead to elevated unbound concentrations. This can lead to toxicity in pregnant women with hypoalbuminemia or anemia. Hence, dosing adjustments are usually not recommended for pregnant women. However, after delivery the bioavailability of tacrolimus returns to normal thereby resulting in higher trough levels at the same dosage. This may even require dose reduction as was seen in two of our patients.

Several previous studies have reported a high incidence of preterm delivery.[6–8,14] Preterm delivery might be related to maternal conditions such as hypertension and fetal conditions such as fetal growth restriction. In our series, all except one delivery were full term. In patient 7, stage III IUGR was observed, probably secondary to rubella infection in the second trimester.

Previous studies have shown that cesarean delivery is common among transplant recipients.[6–8] In our study too, cesarean delivery was performed for five of seven pregnancies. The reasons for cesarean section appear to be appropriate indication and not an excuse to elude the stress of a normal delivery in a liver transplant recipient.

In conclusion, stable liver transplant recipients with stable graft function and on tacrolimus monotherapy have a favorable outcome. There is a physiological reduction of tacrolimus trough levels during pregnancy for which dose augmentation is not usually required.

## AUTHORS CONTRIBUTION

S. S. contributed to acquisition of data and drafting of manuscript. J. S. M. contributed to interpretation of data and draft writing. S. S. contributed to interpretation of data and critical revision of manuscript. U. D. P. contributed to interpretation of data and critical revision of manuscript. All authors approved the final version of the manuscript.

## CONFLICTS OF INTEREST

The authors have none to declare.

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