

Received: 2019.11.05  
Accepted: 2020.02.23  
Available online: 2020.04.24  
Published: 2020.06.09

# Pregnancy Outcomes Following Pediatric Liver Transplantation: A Single-Center Experience in Japan

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Statistical Analysis C  
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**Source of support:** Departmental sources

**Background:** The number of pregnancies after liver transplantation (LT) is increasing; however, the safety and incidence of complications associated with these pregnancies are still unclear. In this report, we retrospectively assessed the influences and problems associated with post-transplant pregnancy on allografts, recipients, and fetuses.

**Material/Methods:** A total of 14 pregnancies were identified in 8 female recipients between 2005 and 2018. The original disease was biliary atresia in all recipients. We provide a basic guide for the management of planned pregnancies in female recipients.

**Results:** Of the 7 planned pregnancies, no recipients took mycophenolate mofetil (MMF) or had allograft liver dysfunction. Among the 7 unplanned conceptions, we judged that the pregnancy was inadequate to continue in 4 recipients due to taking MMF and 2 recipients due to allograft liver dysfunction at conception. However, 4 recipients who immediately stopped taking MMF continued with their pregnancies. Ten pregnancies resulted in live 11 births. Among obstetric complications or fetal and neonatal complications, gestational diabetes mellitus in 3 recipients was the most common. There were 3 miscarriages and 1 planned termination because of MMF medication and liver dysfunction.

**Conclusions:** Planned pregnancies in LT recipients can lead to the birth of a healthy baby and no influence on either the allograft or the recipient. However, unplanned pregnancies in LT recipients, such as recipients who take MMF or have allograft liver dysfunction, may have an adverse influence on the fetus.

**MeSH Keywords:** **Immunosuppression • Liver Transplantation • Pregnancy, Unplanned**

**Abbreviations:** **ACR** – acute cellular rejection; **AZA** – azathioprine; **BA** – biliary atresia; **CS** – cesarean section; **CyA** – cyclosporine; **eCS** – emergency cesarean section; **GDM** – gestational diabetes mellitus; **LT** – liver transplantation; **MMF** – mycophenolate mofetil; **mPSL** – methylprednisolone; **NRFS** – nonreassuring fetus status; **PDA** – patent ductus arteriosus; **Tac** – tacrolimus; **TTN** – transient tachypnea of the newborn; **VD** – vaginal delivery

**Full-text PDF:** <https://www.annalsoftransplantation.com/abstract/index/idArt/921193>

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## Background

Now that liver transplantation (LT) has become an effective, safe, and prevalent treatment for acute chronic liver failure or end-stage liver disease worldwide, an important issue for liver recipients is how to live their life after LT. One of the most serious concerns for female recipients of reproductive age is pregnancy [1].

In Japan, a total of 9242 LTs (8795 living-donor LTs and 447 deceased-donor LTs) were reported until the end of 2017; of these, a total of 2488 recipients (2401 living-donor LTs and 87 deceased-donor LTs), which account for 26.9% of all LTs, were women between the ages of 0 and 39 years at the time of LT [2]. In an investigation in 2014, 38 pregnancies in 30 recipients resulted in 31 live births for 25 recipients in Japan [3]. Although some reports have described post-LT pregnancies associated with acute cellular rejection (ACR), preeclampsia, and other complications, the incidence of these complications is controversial [4–7]. Currently, there are limited data on pregnancy after LT in Japan, and practical guidelines have not yet been established. In this report, we retrospectively assessed the influences on and problems associated with post-transplant pregnancy for allografts, recipients, and fetuses.

## Material and Methods

### Patients

We conducted a retrospective study of pregnancies in recipients who underwent LT at the Department of Surgery, Division of Gastroenterological, General and Transplant Surgery, Jichi Medical University, Japan, and other facilities. We analyzed 8 recipients who gave birth at either the Jichi Medical University Hospital or other hospitals between 2005 and 2018. Approval

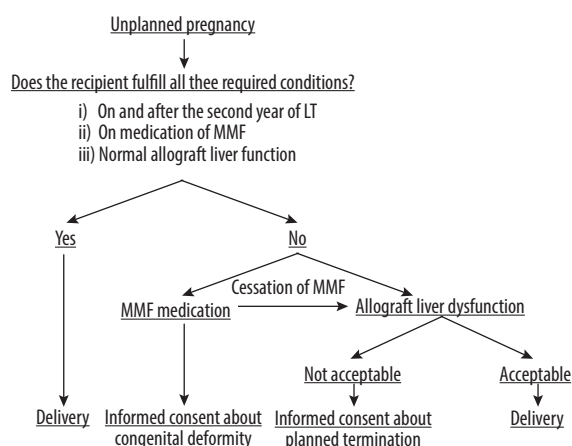
to conduct this study was obtained from the Ethics Committees of Jichi Medical University (Ethics Committee Approval Case Number 15-106).

### Post-transplant immunosuppression therapy

Currently, in our department, the prevalent medication after LT to prevent ACR is a dual-drug combination of tacrolimus (Tac) and methylprednisolone (mPSL). For patients who are at high risk for ACR, such as an ABO-incompatible recipient, mycophenolate mofetil (MMF) is added after steroid pulse therapy. If kidney dysfunction appears as an adverse effect, then Tac is switched to cyclosporine (CyA).

### Management of pregnant recipients and follow-up during gestation

Here, we provide a basic guide for planned pregnancies in female recipients, which requires the following 3 conditions: i) on and after the second year of LT, ii) no MMF medication, and iii) normal allograft liver function. If these 3 criteria were satisfied, then we judged the pregnancy to be medically acceptable. For medically acceptable planned pregnancies, the pregnancy management was conducted at both the Jichi Medical University Hospital and a perinatal medical center. In addition to normal prenatal examinations, blood tests for liver function were needed. Our strategy for unplanned pregnancies is illustrated in Figure 1. When the recipients did not fulfill all 3 of our required criteria within unplanned pregnancies, we conducted normal delivery if allograft liver dysfunction was not present. When the recipients had received MMF, we investigated whether cessation of MMF would be appropriate. If there is allograft liver dysfunction after cessation of MMF, we suggest planned termination. If cessation of MMF is impossible, we suggest planned termination.



**Figure 1.** Our strategy for managing unplanned pregnancy.  
LT – liver transplantation;  
MMF – mycophenolate mofetil.

**Table 1.** Clinical maternal backgrounds.

Patient, number of pregnancy	Indication for LT	Age at LT	Age at conception	Period between LT and pregnancy (years)	Planned or unplanned pregnancy	Immuno-suppressive medication at conception	Immuno-suppressive treatment during pregnancy	Liver dysfunction at conception
A	BA	11	30	20	Planned	None	None	None
			36	25	Planned	None	None	None
B	BA	0.8	26	25	Planned	Tac	Tac	None
			27	26	Planned	Tac	Tac	None
C	BA	9	23	14	Unplanned	Tac+mPSL	Tac+mPSL	○
			26	15	Unplanned	Tac+mPSL	Tac+mPSL	None
			28	20	Unplanned	Tac+mPSL+MMF	Tac+mPSL	None
			4/5	33	24	Planned	Tac+mPSL	Tac+mPSL
D	BA	8, 22	27	5	Planned	Tac+mPSL	Tac+mPSL	None
E	BA	9	25	16	Unplanned	CsA+mPSL+MMF	CsA+mPSL	○
			28	19	Planned	CsA+mPSL	CsA+mPSL	None
F	BA	4	17	13	Unplanned	Tac+MMF	None	None
G	BA	18	25	7	Unplanned	Tac+AZA+mPSL	Tac+AZA+mPSL	○
H	BA	15	20	5	Unplanned	Tac+mPSL+MMF	Tac+mPSL	○

LT – liver transplantation; BA – biliary atresia; Tac – tacrolimus; mPSL – methylprednisolone; MMF – mycophenolate mofetil; CsA – cyclosporine; AZA – azathioprine.

## Results

A total of 14 pregnancies were identified in 8 female recipients. The clinical information related to maternal background is given in Table 1. The original disease was biliary atresia (BA) in all recipients. The median age at LT was 9.0 years old (range, 0.8–22.0 years). One recipient required a second LT (case D). The median age at conception was 27 years old (range, 17–36 years). The median transplant–pregnancy interval was 18 years (range, 5–27 years). Of the 14 pregnancies, 7 were planned pregnancies and 7 were unplanned pregnancies. With all planned pregnancies, no recipients were taking MMF or had allograft liver dysfunction. Conversely, among the unplanned pregnancies, we medically judged that the pregnancy was inadequate to continue in 6 recipients; 2 recipients (14.3%) took MMF and had allograft liver dysfunction at the time of conception, 2 recipients (14.3%) took MMF, and 2 recipients (14.3%) had allograft liver dysfunction. However, 4 recipients who immediately stopped taking MMF continued with their pregnancies.

The outcomes of the pregnancies and the complications of both the recipient and fetus are described in Table 2. Ten pregnancies (11 babies; including 1 set of twins, patients C4 and 5)

resulted in live births. Three miscarriages and 1 planned termination were described. There were 6 cases of vaginal delivery, 3 cases of cesarean section (CS), and 1 case of emergency CS. The median gestation at delivery was 39 weeks (range, 37–41 weeks). The median birthweight was 2844 g (range, 1960–3046 g). Gestational diabetes mellitus (GDM) was the most common obstetric complication, and was observed in 3 recipients. In total, 1 case of atonic hemorrhage and 1 case of nonreassuring fetus status were identified. Preeclampsia was not observed. The fetal and neonatal complications included inguinal hernia, patent ductus arteriosus, transient tachypnea of the newborn, and cryptorchidism. No liver dysfunction, including ACR, was observed during gestation.

## Discussion

Based on the results of the recipients in a single LT center, the live birth rate was 71%. This rate was approximately equal to the 50.0–80.7% reported in the past [8,9]. The planned pregnancies all resulted in live births without any severe complications. This indicates that planned pregnancies can more safely achieve live births without severe complications than unplanned pregnancies. Our strategy for planned pregnancies

**Table 2.** Outcomes of complications of both the recipients and fetuses.

Patient, Number of pregnancy	Planned or unplanned pregnancy	Outcome	Mode of delivery	Gestational age at delivery (weeks)	Birthweight (g)	Obstetric complications	Complications related to LT	Fetal complications	
A	1	Planned	Live birth	VD	40	2998	None	None	None
	2	Planned	Live birth	VD	40	2868	None	None	None
B	1	Planned	Live birth	VD	39	3004	Atonic hemorrhage	None	None
	2	Planned	Live birth	eCS	39	2844	NRFS	None	None
	1	Unplanned	Live birth	VD	39	2623	Uncertainly	None	None
	2	Unplanned	Miscarriage	–	–	–	None	–	–
C	3	Unplanned	Live birth	VD	39	2565	Uncertainly	Small bowel obstruction	None
	4/5	Planned	Live birth	CS	37	1980/1960	GDM, anemia before conception	None	None/inguinal hernia, PDA
D	1	Planned	Live birth	CS	38	2868	GDM	None	TTN, cryptorchidism
E	1	Unplanned	Planned termination	–	–	–	None	None	–
	2	Planned	Live birth	CS	38	3046	GDM	None	None
F	1	Unplanned	Live birth	VD	41	2772	None	None	None
G	1	Unplanned	Miscarriage	–	–	–	None	None	–
H	1	Unplanned	Miscarriage	–	–	–	None	None	–

LT – liver transplantation; VD – vaginal delivery; CS – cesarean section; eCS – emergency cesarean section; NRFS – nonreassuring fetus status; GDM – gestational diabetes mellitus; PDA – patent ductal arteriosus; TTN – transient tachypnea of the newborn.

requires the following 3 criteria: i) on and after the second year of LT, ii) no medication with MMF, and iii) normal allograft liver function. If these 3 conditions were satisfied, then we judged the pregnancy to be medically acceptable. Pregnancy management should be performed at the perinatal medical center and the liver transplant facility. Normal prenatal examinations, including ultrasonography, blood pressure measurements, and urine examinations, were performed each month until gestational week 24, every 2 weeks between gestational weeks 24 and 35, and every week after gestational week 35. In addition, liver function examinations were conducted every month. Jabiry-Zieniewicz et al. reported the importance of preparation and counseling before conception [10]. Education for planned pregnancies can be effective not only for the current pregnancy but also for the next pregnancy in case of spontaneous abortion. These results suggest the need for dedicated efforts with multidisciplinary support for recipients of reproductive age sometime soon after the LT, including appropriate contraception advice, and adjustment to the immunosuppressive treatment in preparation for pregnancy.

Kubo et al. found that pregnancies in the early-interval group (less than 3 years after LT) were significantly more likely to have limited fetal growth, preeclampsia, and extremely low birth weight [4]. However, because we treated mainly pediatric recipients, we could not determine how long the proper periods between LT and pregnancy should be since there were such long periods. An interval of at least 2 years from LT might be needed, as there is unstable liver function within the 2-year period after LT [7].

The 3 miscarriages (21%) in this report were all unplanned pregnancies, and 2 of 3 recipients were taking MMF at conception. The general incidence of spontaneous abortion in Japan is 15% [11]. To prevent spontaneous abortion and congenital deformities, MMF must not be recommended for recipients trying to reproduce, based on the results described by past reports [10,12,13]. Therefore, a pregnancy management strategy is proposed for unplanned pregnancies, as shown in Figure 1. According to the report by Christopher et al., there were no statistically significant differences in pregnancy results between women taking Tac and those taking CyA [14].

Tac is recommended to control ACR when there is an appropriate blood concentration [15,16]. Contrary to previous studies, ACR, preeclampsia, and low birthweight caused by severe allograft liver dysfunction fortunately did not occur in any of the recipients [4–7]. Generally, ACR is likely to occur within 1 year after LT, suggesting that no ACR occurred in our recipients after sufficient intervals from LT. However, because a certain degree of preeclampsia and low birthweight occurred even after intervals of 3 years or more from LT in past studies, we cannot explain our results based only on the time interval. GDM, which occurs in 12% of all Japanese pregnancies, was found in 3 cases in this study [17]. Since Tac also has an effect on insulin production, diabetes is likely to occur after LT or with mPSL [18]. There is a possibility that GDM may be caused by metabolic changes during pregnancy in addition to immunosuppressive treatment.

While the outcomes of the pregnancies were favorable in this report, the safety of breastfeeding during immunosuppressive treatment remains unclear. In our research, immunosuppressive

agents after delivery were not considered. Women traditionally avoided breastfeeding while taking immunosuppressive agents, such as Tac. Bramham et al. reported that the intake of Tac via breast milk could be inconsequential [19]. Studies on the appropriate selection and concentration of immunosuppressive agents are required to better understand the pathophysiology involved.

## Conclusions

Planned pregnancies in LT recipients can lead to the birth of a healthy baby and no influences on the allograft and recipient. However, unplanned pregnancies in LT recipients, such as recipients who take MMF or have allograft liver dysfunction, may have an adverse influence on the fetus.

## Conflict of interest

None.

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