

## Successful Pregnancies in Two Orthotopic Liver Transplant (OLT) Recipients in Iran; Two Case Reports

Tayebi, Zahra (M.Sc.)<sup>1\*</sup>; Taqhavi, Seyyed Alireza (M.D.)<sup>2</sup>; Shahbazi, Shirin (M.Sc.)<sup>3</sup>

1- Namazi Educational Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.

2- Department of Gastroenterology, Shiraz University of Medical Sciences, Shiraz, Iran.

3- Department of Midwifery, Faculty of Nursing and Midwifery, Islamic Azad University of Varamin-Pishva, Varamin, Iran.

### Abstract

**Introduction:** Pregnancy and parenting have been part of human life throughout history and liver transplant recipients are not any exception. This paper reports successful pregnancies in two liver transplant recipients in Iran.

**Case Presentation:** The first case was a 34-year old woman who had undergone orthotopic liver transplantation (OLT) at Shiraz Namazi Educational Hospital in 2002. She decided to get pregnant seven years after the operation. During pregnancy, immunosuppressive therapy continued, except Mycophenolate Mofetil which has an absolute contra-indication in pregnancy. The patient was followed up during pregnancy by the transplant team as well as a gynecologist. She faced no significant complications and the liver function was stable during pregnancy. She later underwent a Cesarean section in the 38<sup>th</sup> week of gestation and the newborn was a healthy girl weighing 2480g with an Apgar score of 8 at the time of birth. There were no evidences of prematurity or structural abnormalities in the newborn. The second case was a 31-year old primipara who had received an orthotopic liver transplant (OLT) in Shiraz in 2002. She had a smooth pregnancy without any complications and the newborn was a boy weighing 3100g with Apgar scores of 8 and 10 at the time of birth and 5 minutes thereafter, respectively.

**Conclusion:** As the number of transplant recipients is growing along with the number of recipients who are in their fertility years, it is vital to ensure a proper medical care by a coordinated multidisciplinary team during pregnancy.

**Keywords:** Cyclosporine, Immunosuppression, Liver transplantation, Mycophenolate Mofetil, Pregnancy.

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\* Corresponding Author:  
Zahra Tayebi, Namazi  
Educational Hospital,  
Shiraz University of  
Medical Sciences, Shiraz,  
Iran.  
E-mail:  
t\_268@hotmail.com

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### Introduction

Liver transplant has turned to an acceptable treatment option for patients with liver failure, although it was previously just an experimental operation conducted on patients with no hope of cure (1). Until 1980, the possibility of living a year after liver transplantation was 30% or even less (2), while presently, it is 90% at the end of the first year and 70% at the end of the 5<sup>th</sup> year following the operation (3).

Parenting is an important factor in improving the quality of life of these patients after liver transplant (4). In female liver transplant recipients, increases in survival rate and improvement of quality of life after transplant are related to the increased number of pregnancies (5).

Pregnancy is usually successful after liver transplant and women with stable liver function can usually handle it well (6,7), but the possibility

of preeclampsia, high blood pressure, low birth weight, prematurity and preterm labor is high among these women (4,6,8).

In a retrospective study on 38 pregnancies from 1992 to 2002 in 29 liver transplant recipients at New York Medical Center, the mean gestational age at the time of birth was 36.4 weeks and the mean weight of newborns was 2762g. There were four incidences of spontaneous abortion during the first trimester and 10 pregnancies were aborted in early stages due to liver dysfunction. The observed complications during pregnancy were diabetes, anemia, preterm labor, preeclampsia, hypertension and severe liver tissue rejection episodes (9).

The first liver transplant in Iran was conducted in 1993 and there have been about 650 transplants of this kind so far. Among these recipients, 250 have been female and more than 80% are in their fertile years. The increasing number of patients with end-stage liver disease who undergo liver transplant as their last resort for treatment and the importance of improving the quality of life of these recipients necessitate considering the role of parenting more seriously. This report describes the first cases of successful pregnancy in female liver transplant recipients in Iran and it can doubtlessly serve as a good example for patients with similar condition and their medical teams.

### Case Presentation

**Case One:** The patient was a 34-year old woman (G<sub>2</sub> P<sub>2</sub>L<sub>2</sub>) who suffered from liver failure due to Wilson's disease. She had orthotopic liver transplant at Namazi Educational Hospital in Shiraz in 2002. After the transplant, liver function was stable and the patient had no rejection episodes or any other complication such as cholestasis.

Conception took place seven years after the operation. This timing had been determined by the transplant team to assure a competent liver function. The patient had a past history of a successful pregnancy before the disease onset and had given birth to a daughter who was 12 at the time of the study.

The transplant team was informed about the pregnancy at the end of the 12<sup>th</sup> week of gestation. The patient had been taking 200mg of Cyclosporine, and 1g of Mycophenolate Mofetil (Cell Cept) per day in the meantime. The Mycophenolate Mofetil intake was terminated and cyclo-

sporine dosage was increased to 300mg per day. Liver function tests and blood concentration of cyclosporine were evaluated periodically. The tests were all normal.

Sonography and gynecological examinations showed a natural fetal growth despite worries about the intake of Mycophenolate Mofetil during the first weeks of pregnancy.

Caesarean section was performed at the 38<sup>th</sup> week of pregnancy under general anesthesia on June 2, 2009. The newborn was a healthy girl, weighing 2480g with an Apgar score of 8 at the time of birth. There were no signs of congenital anomalies, structural abnormalities or prematurity in the newborn.

**Case two:** The patient was a 31-year old woman (G<sub>2</sub> A<sub>1</sub>I<sub>1</sub>) who had been suffering from liver failure due to Wilson's disease. She had undergone orthotopic liver transplant (OLT) at Namazi Educational Hospital in Shiraz in 2002. She had suffered from common bile duct stricture three years after the transplant and had successfully undergone Endoscopic Retrograde Cholangiopancreatography (ERCP), balloon dilatation and stenting. During the years after the transplant, the patient had been experiencing episodes of liver enzyme increases which had been treated by medical interventions. The liver function was stable at the time she decided to get pregnant. Mycophenolate Mofetil intake was terminated as soon as the transplant team was informed about her decision and the patient took 200mg of cyclosporine and 5mg of Prednisolone per day.

The conception took place 7 years after the transplant. The patient had had a spontaneous abortion three months prior to the present pregnancy.

At the time of conception, the patient was under the supervision of a multidisciplinary team of medical experts, including a gastroenterologist, a gynecologist and transplant nurses for the follow-ups, physical examinations and more importantly, consultations. Liver enzymes, bilirubin and cyclosporine concentrations were normal during pregnancy.

Caesarean section was done at the 38<sup>th</sup> week of pregnancy by spinal anesthesia on June 30, 2009. The newborn was a boy weighing 3100g with Apgar scores of 8 and 10 at the time of birth and 5 minutes thereafter, respectively. There were no

signs of congenital anomalies, structural abnormalities or prematurity in the newborn.

### Discussion

The number of organ transplant recipients who wish to get pregnant has increased with the increase in the number of successful transplantations (7). The National Transplantation Pregnancy Registry (NTPR)<sup>1</sup> has reported 187 pregnancies by 111 female liver transplant recipients with 138 successful cases until 2005 (10). Conception after liver transplant is usually successful if it is treated as a high-risk case by a coordinated medical team composed of medical doctors, midwives and nurses (11).

Secondary amenorrhea is common among premenopausal women suffering from end-stage liver diseases, but most of them will commence regular menses within the first year following the transplant (6). However, most liver transplant centers advise their patients not to get pregnant at least two years after the operation to be absolutely ensured of a competent liver function (4,7,9). Pregnancy planned at least two years after the operation can have fine maternal and neonatal outcomes (12).

Obstetrical complications in liver transplant recipients are more common compared to those in the general population.

Masuyama *et al.* presented a 34-year-old pregnant woman after benefiting from a living related liver transplant (LRLT) in Japan who developed severe preeclampsia and fetal growth restriction (FGR). Her liver function was normal but because of FGR, emergency Cesarean section was performed in the 28<sup>th</sup> week of gestation. The authors have stated that the prevalence of complications in pregnancies following LRLT is similar to those after OLT but liver dysfunction might be more common (13).

There are many worries regarding the mother, the baby and the transplant outcome in these pregnancies. One of the most important concerns is the effort to plan an appropriate drug regimen to suppress the recipient's immune system to assure the fetus's health and also to minimize the risk of rejection episodes during pregnancy (7).

Immune system suppression continues during pregnancy. The same dosage of cyclosporine, Tacrolimus and steroids are usually prescribed before and after pregnancy, but the dosage of Azathioprine is reduced. Mycophenolate Mofetil (MMF) is absolutely contraindicated during pregnancy (6). US Food and Drug Administration (USFDA) changed the pregnancy category of Mycophenolate Mofetil from group C to D in a report published on November 30, 2007. This change was based on the reports of rising abortion risks and increasing risk of structural abnormalities in the newborns during the first trimester. Accordingly, M. Mofetil intake is terminated six weeks before family planning up to the end of pregnancy (14). However, some other studies have shown the safety of this medication during pregnancy albeit these studies have been conducted before 2007. As an example, Guang-Dong Pan *et al.* reported a 22-year-old woman who had undergone orthotopic liver transplant in China in September 2000. She received multidisciplinary care during pregnancy. She was pregnant in the 33<sup>rd</sup> month post-operatively. The patient experienced a rejection episode on the 8<sup>th</sup> week of pregnancy that was successfully treated by Mycophenolate Mofetil with no adverse effects with an eventual birth of a 2000g healthy-looking newborn (12). Armenti *et al.* state that limitations in assessing the risk of congenital malformations upon MMF exposure include a weak methodology, potential reporting biases, small sample sizes, and inability to exclude other co-morbid factors such as non-immunosuppressive drug effects or other susceptibilities in this population (15).

Teratogenic effects have been shown for some other medications with immunosuppressive properties in humans. The rate of structural abnormalities in newborns of liver transplant recipients who are treated by cyclosporine is less than the expected rate for the healthy population (4). On the other hand, some studies have shown an increased risk for cleft lip in the newborns due to intake of steroids during the first trimester of pregnancy. However, in a retrospective study in Hungary, no relationship was found between infant anomalies and consumption of steroids in the second and third months of pregnancy (7).

Obstetrical complications seem to be less common in women who take Tacrolimus instead

1- The National Transplantation Pregnancy Registry (NTPR) was established in 1991 at Thomas Jefferson University, Philadelphia, PA to study the outcomes of pregnancies in female transplant recipients and those fathered by male transplant recipients.

of cyclosporine. The study on 27 pregnancies in 21 female liver transplant recipients who received Tacrolimus showed lower prevalences of high blood pressure and preeclampsia compared to those taking cyclosporine. Moreover, transient kidney failure and hyperkalemia were observed in 36% of the newborn, which were possibly due to maternal Tacrolimus intake (4).

Zieniewicz has reported the outcomes of four successful pregnancies in liver transplant recipients who were taking Tacrolimus. The age range of the patients was 23 to 32 years and the time of conception was 12 to 59 months after transplant. Preterm labor was the main complication in these patients and there was only one severe rejection attack. In spite of the complications, all four pregnancies were successful. The weight range of newborns at birth was 1410 to 3490g and the mean Apgar score was eight. No structural anomalies or prematurity were reported (16).

Christopher *et al.* reported the outcomes of all pregnancies occurring following liver transplant at King's College Hospital, in London, during 1988 to 2004. Seventy-one pregnancies were recorded in 45 recipients; almost all the pregnancies were successful (50 live births) and there were no cases of graft loss during pregnancy. The most common complications during pregnancy were pregnancy-induced hypertension (20%) and preeclampsia (13%). Tacrolimus and cyclosporine were commonly used and there were no statistically significant differences in complication rates observed between the immunosuppressive agents (17).

Despite favorable outcomes mentioned in the aforementioned studies, pregnancy after liver transplantation should be considered as a high risk condition. These patients need close and continuous care by the medical team. Patient monitoring should include frequent liver function tests, assessment of immunosuppressive concentration in blood, fetal monitoring via ultrasonography, regular blood pressure controls and screening for infections. Both mother and her fetus should be tested for Cytomegalovirus too (4, 7).

### Conclusion

Pregnancy after liver transplantation is usually successful. The cases reported here were the first Iranian liver transplant recipients who experienced a successful pregnancy. Although pregnancy in liver transplant recipients is common in

the world but it should be regarded as a high-risk pregnancy that entails close observation and care by an experienced medical team.

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