First successful perinatal management of pregnancy after ABO-incompatible liver transplantation

Hisanobu Higashi, Hideaki Obara, Kei Miyakoshi, Masahiro Shinoda, Minoru Kitago, Naoki Shimojima, Yuta Abe, Taizo Hibi, Hiroshi Yagi, Kentaro Matsubara, Yohei Yamada, Osamu Itano, Ken Hoshino, Tatsuo Kuroda, Yuko Kitagawa

Institutional review board statement: The study was reviewed and approved by the Keio University School of Medicine Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare no conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Correspondence to: Hideaki Obara, MD, PhD, FACS, Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. obara.z3@keio.jp

Abstract

Many papers have reported on pregnancy and delivery after liver transplantation, but there have been no reports on pregnancy after ABO-incompatible liver transplantation. This paper reports the first successful pregnancy and delivery of a newborn after ABO-incompatible liver transplantation for fulminant hepatic failure. The patient was a 39-year-old female. She had an ABO-incompatible liver transplantation, donated from her husband, due to subacute fulminating hepatitis of unknown etiology. She was taking tacrolimus, methylprednisolone, and mizoribine orally for the maintenance of immunosuppression at the time of discharge. She was discharged uneventfully on postoperative day 38 without any rejection episodes. At 1 year and 6 mo after transplantation, she indicated a wish to become pregnant. Therefore, treatment with mycophenolate mofetil was interrupted at that time. After two miscarriages, she finally became pregnant and delivered transvaginally 3 years after the transplantation. All of the pregnancies were conceived naturally. The newborn was female with a birth weight of 3146 g; the Apgar scores were 9 and 10. Delivery was performed smoothly, and the newborn exhibited no malformations. The mother and the newborn were...
discharged uneventfully. We suggest that pregnancy should be allowed for those who previously received ABO-incompatible liver transplantation.

Key words: Pregnancy; Liver transplantation; Delivery; Fulminant hepatic failure; ABO-incompatible; Living donor

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This report is on the first successful perinatal management of pregnancy after ABO-incompatible liver transplantation. We suggest that pregnancy should be allowed for those who previously received ABO-incompatible liver transplantation.

Higashi H, Obara H, Miyakoshi K, Shinoda M, Kitago M, Shimojima N, Abe Y, Hibi T, Yagi H, Matsubara K, Yamada Y, Itano O, Hoshino K, Kuroda T, Kitagawa Y. First successful perinatal management of pregnancy after ABO-incompatible liver transplantation. World J Gastroenterol 2017; 23(3): 547-550. Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i3/547.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i3.547

INTRODUCTION

Liver transplantation has been established as a medical treatment for end-stage liver disease patients. In Japan, living-donor liver transplantation, including ABO-incompatible liver transplantation, is the most available procedure due to a chronic lack of deceased donor livers. We established a protocol for ABO-incompatible liver transplantation that uses immunosuppressants (e.g., cyclosporin or tacrolimus), rituximab, steroids, mizoribine, and intraportal infusion therapy[1,2]. Although there are extensive operative stresses involved and immunosuppressants are required, many papers have reported a successful pregnancy or delivery after liver transplantation[3,4]. However, only two reports described pregnancy and delivery after ABO-incompatible kidney transplantation, and there have been no reports on pregnancy after ABO-incompatible liver transplantation[5,6]. This paper reports the first successful pregnancy and delivery of a newborn after ABO-incompatible liver transplantation for fulminant hepatic failure.

CASE REPORT

A 39-year-old woman, gravida 1, para 1, received an ABO-incompatible liver transplantation, donated from her husband. The transplantation was due to subacute fulminant hepatitis that occurred two months after her first delivery; although the etiology was unknown, it was suspected to be drug-induced. She had no appreciable diseases, including hepatitis virus infections, or a past or family history of liver disease. She was allergic to crab butter but not any medicines. Her blood type was O, Rh(+), and her HLA-A, B, DR was A2/A11, B35/B55, DR9/DR12. The donor’s blood type was A, Rh(+), and his HLA-A, B, DR was A2/A24, B46/B48, DR8/DR16. Her anti-A and anti-B antibodies before hepatitis were uncertain due to a plasma exchange (PE).

She gave birth to her first baby by vaginal delivery at the age of 39 years old in February 2012. After delivery, she suffered from refractory periodontitis; she took the antibiotic cephem (cefdinir) for 6 d starting in April 2012 because of the periodontitis. Subsequently, she exhibited general malaise, general itching sensations, and chills. A dermatologist prescribed levocetirizine and prednisolone unguent, but the symptoms persisted with no improvement. She also had a problem with a second premolar tooth because she had exodontia and took the antibiotic cephem (cefdinir) to prevent infection. However, after taking this antibiotic, she experienced the sudden onset of jaundice and severe hepatic dysfunction [aspartate transaminase (AST)/alanine aminotransferase (ALT) = 948/1090 IU/L, T-Bil 138 μmol/L, D/T = 0.71, prothrombin time-international normalized ratio (PT-INR) = 1.00]. She was admitted to the hospital with fulminant hepatitis of unknown etiology, and liver support therapy was performed. A liver biopsy revealed acute, drug-induced hepatitis. Her liver function continued to deteriorate [AST/ALT = 944/1114 IU/L, T-Bil 296 μmol/L, D/T = 0.76, PT-INR = 1.23], and she developed hepatic encephalopathy two weeks later, when the first symptoms appeared. On the day hepatic encephalopathy appeared, she was transferred to our hospital. We performed PE five times and started continuous hemodiafiltration. The first PE was fresh frozen plasma of blood type O, and the others were blood type AB due to the possibility of ABO-incompatible liver transplantation. Although she was registered on the waiting list for deceased donor liver transplantation in Japan, the progression of liver dysfunction did not allow for much time to be spent waiting for a deceased liver donation [the model for end-stage liver disease (MELD) score increased from 28 to 36 in a week]. In addition, pancreatitis was suspected due to the PEs because of the elevation in serum amylase. An ABO-incompatible liver transplantation was performed 10 d after the first PE was performed; the liver was donated from her 33-year-old husband. Before transplantation, her anti-A antibodies were 64 × (IgM) and 128 × (IgG), and her anti-B antibodies were 32 × (IgM) and 64 × (IgG).

The donor’s left liver lobe (graft weight; 452 g, graft weight/recipient body weight = 0.93) was transplanted, and a splenectomy was also performed along with the insertion of an intraportal infusion catheter and immunosuppression, according to our protocol[4] for ABO-incompatible liver transplantation. Rituximab was infused one time just after the liver transplantation. The operation time was 10 h and 18 min, and blood loss was 538 mL.
Her encephalopathy improved promptly after the transplantation. She was extubated on postoperative day (POD) 3 and discharged from the intensive care unit on POD 7. Tacrolimus, steroids, and mizoribine were given, and intraportal infusion therapy was performed to prevent rejection (Figure 1). The jaundice and liver function gradually improved, and she was discharged from the hospital on POD 38 with no bacterial infections or rejection episodes (laboratory data at the time of discharge: AST/ALT = 18/16 IU/L, T-Bil 15 μmol/L, D/T = 0.11, PT-INR = 1.08).

When she was discharged, she was taking tacrolimus (1.4 mg/d), methylprednisolone (mPSL; 15 mg/d), and mizoribine (200 mg/d) orally for the maintenance of immunosuppression, and her anti-A and anti-B antibodies were not increased; anti-A antibodies: 32 × (IgM) and 256 × (IgG), anti-B antibodies: 32 × (IgM) and 64 × (IgG). Although she developed steroidal diabetes, it was well controlled with insulin (HbA1c was within the range of 5.2%-6.1% during pregnancy).

Her serum tacrolimus concentration was maintained between 3 ng/mL and 8 ng/mL as an outpatient. Her general condition improved gradually, and 1 year and 6 mo after transplantation, she expressed a desire to become pregnant. Thereafter, she conceived spontaneously but miscarried twice, 2 years and 2 years plus 6 mo after the transplantation. Three years after the transplantation, when she was 42 years old, she conceived spontaneously, and the perinatal clinical course was uneventful. At the 39th week of pregnancy, a female baby weighing 3146 g was delivered vaginally with Apgar scores of 9 and 10 at 1 and 5 min, respectively. The intra- and postpartum courses were uneventful, and there was no postpartum hemorrhage. The baby exhibited no malformations and was healthy at the age of 6 mo. During the course of pregnancy, she took 4 mg/d of tacrolimus without reduction or suspension, and her levels of AST, ALT, and bilirubin remained within normal ranges. In addition, her anti-A and anti-B antibody levels were stable during the perinatal period: antenatal: anti-A antibodies: 2 × (IgM) and 16 × (IgG); anti-B antibodies: 32 × (IgM) and 64 × (IgG); postnatal: anti-A antibodies: 2 × (IgM) and 8 × (IgG), anti-B antibodies: 16 × (IgM) and 64 × (IgG). Although the blood type of the baby was uncertain, anti-A and anti-B antibodies did not increase during the pregnancy.

**DISCUSSION**

ABO-incompatible living-related liver transplantation is a procedure that is performed to resolve the lack of deceased donors. Due to the immunosuppression protocol for ABO-incompatibility comprising rituximab[1], it has become a relatively straightforward procedure. Our protocol for ABO-incompatible liver transplantation has allowed patients to undergo transplantation with a prognosis similar to that of an ABO-compatible liver[7]. This procedure greatly increases the likelihood of a successful transplantation in acute liver dysfunction patients who could not find an ABO-compatible donor. Indeed, in this case, the only donor available within the limited time was ABO incompatible. In the past, the survival rate of ABO-incompatible liver transplantation...
was lower than that of ABO-compatible transplantation, but with improvements, there is currently no significant difference between ABO-compatible and ABO-incompatible transplantation in the Japanese registry[9,10]. Many papers have reported obstetric complications during pregnancy after liver transplantation; liver dysfunction and preclampsia are commonly reported according to systematic reviews[9,10]. The rates of cesarean section and preterm delivery are also higher after liver transplantation than in the general population; accordingly, gestational age is shorter after liver transplantation than in the general population. Fortunately, the perinatal course in our patient was uneventful. In contrast to previous reports[9,10], the patient delivered an appropriate-for-date newborn at full term.

Immunosuppression is an important point in pregnancy. The interruption of mizoribine use prevented teratosis, and no liver dysfunction was observed. Because mycophenolate mofetil was used, the patient needed a six-month interval before the pregnancy because of its teratogenic effects.

In conclusion, we experienced and reported the first successful management of a case of pregnancy after ABO-incompatible liver transplantation for fulminant hepatic failure.

**Related reports**
There have been no reports on pregnancy and delivery after ABO-incompatible liver transplantation.

**Term explanation**
ABO-incompatible liver transplantation is a type of living-donor liver transplantation.

**Experiences and lessons**
This case suggests that the possibility of pregnancy for recipients of ABO-incompatible liver transplantation is equivalent to that for recipients of ABO-compatible liver transplantation.

**Peer-review**
This is a brief report of a successful pregnancy after ABO incompatible liver transplantation. The manuscript is well written and would be of interest to the readers of this journal, the references are up to date.

**REFERENCES**

1. Tanabe M, Shimazu M, Wakabayashi G, Hoshino K, Kawachi S, Kodomura T, Seki H, Morkaya Y, Kitajima M. Intraportal infusion therapy as a novel approach to adult ABO-incompatible liver transplantation. *Transplantation 2002; 73: 1959-1961* [PMID: 12131697]

2. Mishina K, Obara H, Sugita K, Shinoda M, Kitago M, Abe Y, Hibi T, Yagi H, Matsubara K, Mori T, Takano Y, Fujiwara H, Itano O, Hasegawa N, Iwata S, Kitagawa Y. Helicobacter cinaedi bacteremia with cellulitis after ABO-incompatible living-donor liver transplantation: Case report. *World J Gastroenterol 2015; 21: 7911-7915* [PMID: 26167092 DOI: 10.3748/wjg.v21.i25.7911]

3. Nagy S, Bush MC, Berkowitz R, Fishbein TM, Gomez-Lobo V. Pregnancy outcome in liver transplant recipients. *Obstet Gynecol 2003; 102: 121-128* [PMID: 12850617 DOI: 10.1016/s0029-8444(03)00369-7]

4. Kainz A, Harabuzc I, Cowlrick IS, Gadgil S, Hagiwara D. Analysis of 100 pregnancy outcomes in women treated systemically with tacrolimus. *Transpl Int 2000; 13 Suppl 1: S299-S300* [PMID: 11112018]

5. Takahashi K, Sonda K, Okuda H, Nakazawa H, Kawaguchi H, Toma H, Agishi T, Ota K, Nakabayashi M, Takeda Y. The first report of a successful delivery in a woman with an ABO-incompatible kidney transplantation. *Transplantation 1993; 56: 1288-1289* [PMID: 8290142]

6. Exposito L, Rostaing L, Kumar S. Successful pregnancy after ABO-incompatible kidney transplantation. *Transpl Int 2016; 29: 506-507* [PMID: 26615059 DOI: 10.1111/tri.12724]

7. Tanabe M, Kawachi S, Obara H, Shinoda M, Hibi T, Kitagawa Y, Wakabayashi G, Shimazu M, Kitajima M. Current progress in ABO-incompatible liver transplantation. *Eur J Clin Invest 2010; 40: 943-949* [PMID: 20636381 DOI: 10.1111/j.1365-2362.2010.02339.x]

8. Umesita K, Inomata Y, Furukawa H, Kasahara M, Kawasaki S, Kobayashi E, Kokudo N, Sakaie S, Shimada M, Tanaka E, Uemoto S. Liver transplantation in Japan -Registry by the Japanese Liver Transplantation Society. *Hepatol Res 2016; 46: 1171-1186* [PMID: 26887781 DOI: 10.1111/hepr.12676]

9. Deshpande NA, James NT, Kucirka LM, Boyarsky BJ, Garonzik-Wang JM, Cameron AM, Singer AL, Dagher NN, Segev DL. Pregnancy outcomes of liver transplant recipients: a systematic review and meta-analysis. *Liver Transplant 2012; 18: 621-629* [PMID: 22344967 DOI: 10.1002/lt.23416]

10. Dei Malatesta MF, Rossi M, Rocca B, Iappelli M, Giorno MP, Berloco P, Cortesini R. Pregnancy after liver transplantation: report of 8 new cases and review of the literature. *Transpl Immunol 2006; 15: 297-302* [PMID: 16635752 DOI: 10.1016/j.trim.2006.01.001]

**P- Reviewer:** Kumar R, Quak SH, Ramsay MA  
**S- Editor:** Yu J  
**L- Editor:** A  
**E- Editor:** Liu WX
