

Case Report

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Successful liver transplantation and delivery in a woman with fulminant hepatic failure occurring during the second trimester of pregnancy

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Abstract: *Background:* Severe liver dysfunction occurring during pregnancy is an unusual but dramatic event that poses special technical and ethical issues because it involves two lives. *Methods and Results:* We report the case of a 35-year-old woman with cryptogenic fulminant hepatic failure who underwent successful orthotopic liver transplantation at 22 weeks of pregnancy. After a relatively uneventful post-operative course she delivered a normal offspring at the 27th week of gestation. There were no obstetrical complications and neonatal outcome was excellent. After a year of follow-up, the patient is doing well, and the newborn has exhibited normal psychomotor and weight/height development. *Conclusion:* This case illustrates the challenge of treating fulminant hepatic failure during pregnancy and demonstrates that liver transplantation is a feasible therapeutic option for treatment of patients with this condition, allowing successful completion of pregnancy.

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The occurrence of fulminant hepatic failure (FHF) during pregnancy is a dramatic clinical event that may result from several diseases (1–3). Some of them are unique to pregnancy, such as the HELLP syndrome, acute fatty liver of pregnancy and preeclampsia (4), while other conditions are similar to those seen in the non-pregnant population (5). The former group of diseases typically occurs at the third trimester of gestation and early delivery is indicated if severe liver dysfunction is present, which may prevent perinatal mortality (4, 6). On the other hand, when FHF occurs during the first or second trimester of pregnancy, particularly before 24th week, the fetus has little possibilities of survival after delivery. Thus, liver transplantation, if indicated, must be performed considering the surgical and medical risks to the fetus, including exposure to immunosuppressive

and various other drugs. Worldwide, there are few reports of liver transplantation performed during the first or second trimester of pregnancy with successful maternal outcomes (7). In addition, most published cases report spontaneous or induced fetal deaths. Here, we present the case of a 22-week pregnant woman with FHF, who underwent an emergency liver transplantation and successfully completed the pregnancy. Perioperative care of the mother and the fetus as well as ethical issues involved in management of this complex case are also discussed.

Case report

A 35-year-old Hispanic pregnant woman presented to us with a history of jaundice and dark urine for the past 3 weeks. Her symptoms started

when she was 15 weeks pregnant. Her previous personal and family medical history was unremarkable. She did not drink alcohol and did not receive any medication other than lactulose for constipation. She had no fever or itching. At physical examination, the patient was found intensely jaundiced, with normal vital signs. She had a functional aortic systolic murmur. The liver was palpable at 1 cm below the costal margin, slightly sensible. Uterine height was 2 cm above the umbilicus. There was no evidence of hepatic encephalopathy or stigmata of chronic liver disease. Laboratory evaluation showed the following: Hematocrit 35.1%, leukocyte count $11.700 \text{ cells/mm}^3$, platelet count $253.000/\text{mm}^3$, ALT 2490 U/L and AST 2063 U/l; alkaline phosphatase 439 U/L and bilirubin 8.8 mg/dl; the International Normalized Ratio (INR) for prothrombin time was 1.17. Serological tests for viral hepatitis A, B, C and E were all negative. Antinuclear antibodies, antismooth muscle antibodies and anti-LKM1 antibodies were all negative. Determination of anti-HIV antibodies was negative. Ceruloplasmin was normal. IgM antibodies to cytomegalovirus and Epstein-Barr were negative. Antibodies anti-parvovirus B19 class IgM were positive, while IgG was negative. An abdominal ultrasonography performed during the initial evaluation was unremarkable.

The patient was discharged with no specific therapy, but was re-admitted at the 22nd week of pregnancy because of marked anorexia and nausea. A marked deterioration was present, with serum total bilirubin reaching a peak value of 28 mg/dL and prolonged prothrombin time (INR = 5). Subsequently, a significant drop in ALT levels was noted, which was associated to a decrease in liver size in a new abdominal ultrasound. She also developed hypoglycemia and progressive somnolence. The diagnosis of FHF was made and since she met King's college criteria (8), she was listed for urgent liver transplantation. Twenty-four hours later, she underwent a successful orthotopic liver transplant using an ABO-identical liver from a donor who died because of massive intracranial hemorrhage. The surgical technique used was a modified Piggy-back side-to-side cavo-cavostomy, end-to-end portal vein and arterial anastomosis (no conduit was used) and duct-to-duct biliary anastomosis. Venous bypass was not used. Special consideration was given to the patient's position during the surgery in order to avoid compression of the inferior vena cava by the pregnant uterus (Fig. 1). The patient remained hemodynamically stable with low transfusion requirements. Two units of packed RBCs, 4 U of fresh frozen plasma

and 300 cm^3 from a cell-saver device were used during the transplant procedure. She was extubated 24 h after transplant. Histological examination of the explanted liver confirmed the presence of massive hepatic necrosis.

Patient and fetus postoperative course was uneventful, with recovery of liver function progressively until day 10 when she presented gradual elevation in total bilirubin. An MRI cholangiography showed a biliary stenosis at the anastomotic level. Therefore, on 14th postoperative day, she underwent a successful Roux-en-Y biliary reconstruction. Immunosuppression was based on methylprednisolone 200 mg/day during the first 3 postoperative days, followed by 10 mg of prednisone plus tacrolimus to achieve a level of 10 ng/ml. Obstetric ultrasonography consistently showed normal fetal growth and anatomy. On 19th postoperative day, a biopsy-proven mild acute cellular rejection was diagnosed and was treated by adjusting tacrolimus serum level to 12–14 ng/dL. She was discharged on her 21st postoperative day. Both patient and donor were seropositive for CMV IgG and surveillance testing to detect CMV infection was conducted every 2 weeks in the first 2 months after transplantation and remained negative.

Forty-three days after transplant, she started showing uterine activity, at 27 weeks of pregnancy. Phenoterol administration was ineffective in stopping labor and she delivered a female baby of 35-cm length and 900 g weight (Apgar score 2-6-8). After 1 day of ventilatory support and 4 days in the intensive care unit the baby remained under standard care for premature infants for 8 weeks, and no further complications were seen. Of note, both renal function and plasma electrolyte

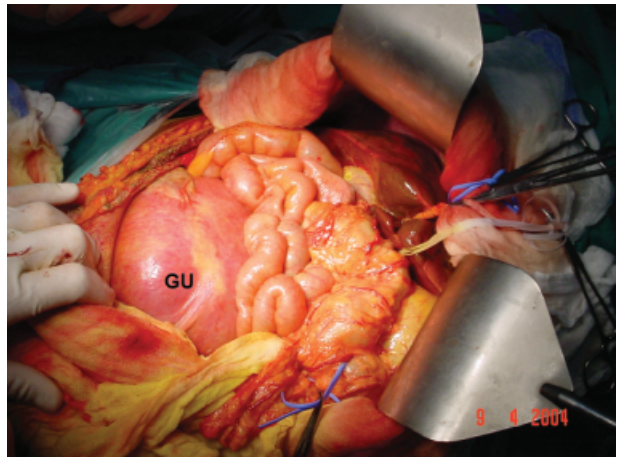


Fig. 1. Laparotomy of an orthotopic liver transplantation performed at 22 weeks of pregnancy. The gravid uterus (GU) and necrotic liver are visualized during the surgical procedure

concentrations remained stable during the early postnatal days. Postpartum serum liver tests of the mother were normal. After a year of follow-up, the patient is in excellent medical condition with normal liver function. The baby has shown normal psychomotor development and corrected weight and height curves are in the 50th percentile.

Discussion

FHF has been reported at any time during pregnancy but appears more frequently during the third trimester due to liver diseases unique to pregnancy (1, 3, 4). Nevertheless, all other causes of FHF could affect pregnant women at any trimester with serious consequences to the mother and the fetus. Cryptogenic FHF is especially frequent during pregnancy with uncertain prognosis for both the mother and the fetus. The etiology of FHF in our patient was unclear. Although she tested positive for antiparvovirus B19 class IgM antibodies, an interpretation of this finding is difficult as the relationship between parvovirus B19 infection and acute hepatitis or FHF is controversial. In fact, a recent study reveals no statistically significant difference in parvovirus B19 DNA detection in liver tissue among patients who had FHF compared with patients with acute viral hepatitis and a control group with non-viral hepatic disease (9). Moreover, parvovirus B19 DNA has been found in 24% of liver tissue and 9% of bone marrow samples in healthy donors (10, 11).

There is little worldwide experience in liver transplantation in pregnant women, with only 11 cases previously reported in the literature (7, 12–16). Cadaveric- and living-related grafts have been used with excellent maternal outcome. Unfortunately, fetal outcomes in published cases have been poor with only three survivors (27%). Reported causes of death range from spontaneous and artificial abortion to neonatal death (7). With regard to survivors, two of them were preterm delivery (28 and 30 weeks). In the present case, no evidence of fetal damage or anomalies was found in repeated examinations, which included ultrasonographic examination and frequent fetal monitoring. Abortion was not considered an option because of ethical considerations of the transplant team and also because of the mother's preferences. All efforts to minimize the use of drugs or anesthetics with potential toxic effects on the fetus were made. In addition, restriction of X-ray examinations, including CT scan, was observed. The immunosuppression scheme and dosage of drugs used in our patient were based on published evidence indicating the

safety of tacrolimus for immunosuppression during pregnancy after liver transplantation (17–20). Preterm delivery and low birth weight seem to be persistent problems in all solid-organ transplantation under any form of immunosuppression (21). However, tacrolimus shows a low rate of onset of hypertension, toxemia of pregnancy, renal function impairment and acute cellular rejection compared with cyclosporine during pregnancy (18). With these considerations, tacrolimus was chosen as the main immunosuppressive agent in our patient and despite the fact that the patient had a preterm delivery (27 weeks) and the baby had low birth weight, they both survived and had no anomalies or complications after 1 year of follow-up after the liver transplant. Of note, no hyperkalemia or renal impairment was noted in the newborn. These complications have been described in up to 36% of babies born from mothers receiving tacrolimus (22).

Alternative management of our patient could have included options such as living-related right lobe liver transplantation (23) and use of an extracorporeal liver support device [i.e., molecular adsorbent recirculating system, MARS] (24). Both options had been successfully used in pregnant patients (7, 25). Fortunately, the rapid availability of a donor liver allowed us to carry out a cadaveric orthotopic liver transplantation with excellent long-term results.

The case presented here is the 12th report of liver transplantation performed during early pregnancy, being the fourth to show a successful mother and fetal outcome. The achievement of this goal involves a multispecialty team approach including hepatologists, transplant surgeons and obstetricians. As in other high-risk pregnancies, close mother and fetal monitoring should be carried out during pregnancy and the puerperium. Antenatal fetal surveillance should be based on fetal heart rate monitoring, ultrasound biometry and doppler blood flow studies of fetal and uteroplacental circulation (26). In addition, careful consideration of potentially toxic effects of drugs as well as excess of X-ray irradiation has to be made. Finally, ethical advice from an ad-hoc committee may be needed to properly balance the health risks of both the mother and the fetus (27).

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