Drugs & the Liver: High Risk Patients & Transplantation

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REPRODUCTION AFTER TRANSPLANTATION

V. Scantlebury and T.E. Starzl

Univerisity of Pittsburgh Department of Surgery
3601 Fifth Avenue Falk Clinic 5 W
Pittsburgh, PA 15213

The success of orthotopic liver transplantation (OLTx) has greatly improved since the introduction of cyclosporine in 1980. Many young patients are given a second chance at life, and with this comes the restoration of menstrual abnormalities and the possibility of pregnancy [1, 2]. Since the first successful pregnancy in a liver transplant patient took place in 1976 [3, 4], a total of 29 babies have been born to 22 liver transplant recipients from the combined programs of the University of Colorado and the University of Pittsburgh. The complications and outcome of these pregnancies are reviewed and the effect on hepatic function is analyzed.

Background

Four patients underwent OLTx at the University of Colorado prior to 1980, while 18 patients received their liver transplantations at the University of Pittsburgh between 1983 and 1990. The indications for transplantation consisted primarily of chronic active hepatitis (10 patients) and fulminant hepatitis (3 patients). Two were transplanted for alpha-1 antitrypsin deficiency and sclerosing cholangitis, while biliary atresia, Wilson's disease, Caroli's disease, primary biliary cirrhosis, secondary biliary cirrhosis and Budd-Chiari Syndrome were the indications in one case each. Immunosuppression consisted of combinations of prednisone, azathioprine and/or cyclosporine in all but one patient who received the new immunosuppressive drug FK506 and prednisone. Two patients were switched from cyclosporine to FK506 1.2 and 6.5 years later.

One patient was transplanted acutely for fulminant hepatic failure during pregnancy, presenting at 26 weeks gestation [5]. All others conceived between 3 weeks and 11 1/2 years after transplantation (Table 1).

TABLE I

CONCEPTION TIME AFTER TRANSPLANTATION

	NO. OF PATIENTS
WITHIN FIRST YEAR	11*
0-6 MONTHS	3*
6-12 MONTHS	7
WITHIN 1 TO 3 YEARS	7
AFTER 3 YEARS	5

* One patient was 26 weeks pregnant at transplantation

The patient who received FK506 and prednisone immediately after OLTx became pregnant within 15 months, but underwent an elective termination of pregnancy. This patient did not deliver any children after OLTx and therefore was not included in this study. Four other abortions after OLTx were reported: two patients each had a spontaneous abortion prior to successfully completing a pregnancy; one other had 2 therapeutic abortions after a difficult pre-term delivery.

Results

Twenty-two recipients of orthotopic liver transplantation delivered 29 children, including 2 sets of twins. Five patients each had 2 successful pregnancies. Eleven babies were born by normal spontaneous vaginal deliver (NSVD), 8 of which were full term babies; three were preterm (27%), delivered before 36 weeks gestational age. Mean birth weight in this group was 2660 grams. Fourteen of the remaining 16 deliveries performed by cesarean section resulted in preterm infants (88%), with a mean

gestational age of 32 weeks. The average birth weight for cesarean births was 1820 grams. Preeclampsia was seen in 5 patients, and was the cause of early delivery in 4 of these (3 by cesarean, 1 by NSVD). Premature rupture of membranes and fetal distress were also included as frequent causes of cesarean deliveries (3 each). Other less frequent precipitating factors were breech presentation (1), transverse lie (1), intrauterine growth retardation (1) and previous cesarean delivery (4).

One repeated antepartum maternal complication seen was anemia, demonstrated in six patients (hemoglobin less than 10g/lb). Two patients were anemic from their first prenatal visit, and required red blood cell transfusions during and after their pregnancies. Progressive hypertension was seen in 2 patients, while recurrent urinary tract infection and pyelonephritis complicated the courses of 2 additional patients.

The alterations in hepatic enzyme function seen in patients are summarized as seen in Table 2. Two patients had biopsy proven rejection in the first and third trimester of pregnancy. The first one underwent treatment with steroids for presumed acute rejection, a diagnosis later changed to chronic rejection. This patient continued to have elevated transaminase enzymes throughout pregnancy. The second patient was diagnosed with acute rejection in the third trimester, biopsy also showing areas consistent with a hepatitic process. Treatment was withheld until after deliver, with near resolution of the abnormal transminases even before steroid therapy was initiated. A third biopsy performed in a patient with hepatitis B, was consistent with mild hepatitis in the second trimester of pregnancy. Four other patients had transaminase enzyme elevations in the antepartum period, and without treatment, resolved spontaneously in the immediate post-partum period. There were no reported changes in hepatic graft function in the remaining fifteen patients.

Progressive increase in hepatic enzyme activity occurred in ten patients in the post-partum period, half of whom had stable hepatic function prior to delivery. Four patients were treated empirically with steroids, while four others underwent a liver biopsy and/or percutaneous transhepatic cholangiogram (PTC).

TABLE II

ALTERATIONS IN LIVER FUNCTIONS

ANTEPARTUM	
STABLE FUNCTION	15
ENZYME ELEVATIONS	7
BIOPSY	3
POST PARTUM	
STABLE	12
ENZYME ELEVATIONS	10
STEROID TREATMENT	4
BIOPSY AND/OR PTC*	4
SPONTANEOUS RESOLUTION	3

*PTC: Percutaneous Transhepatic Cholangiogram

Two patients who had biopsies and PTC's had normal results; one was found to have ongoing hepatitis by biopsy. The fourth patient underwent a PTC after no improvement was seen with steroid treatment, and was found to have multiple biliary structures by cholangiogram. This patient had chronic rejection diagnosed in the first trimester, and underwent re-transplantation within 2 months after delivery.

Of the twenty-nine infants born to women who received liver transplantation, one was conceived 27 weeks prior to an emergency OLTx for fulminant hepatic B. A second OLTx was required on post-op day 3 due to primary graft failure. As a result of multiple complications, a cesarean delivery was carried out 1 week later, with subsequent death of the neonate. Of the remaining 28 babies conceived after transplantation, a second death occurred in an infant born at 26 weeks gestation, whose mother developed severe preeclampsia. This child died from presumed sepsis after becoming neutropenic [5]. A third death occurred in a 7 month old infant born to a patient 10 years after her transplant and 3 1/2 years after the birth of her first child [6]. A diagnosis for the human immunodeficiency virus infection was made in both mother and child, both of whom later succumbed to the complications of this virus infection. One other maternal death was reported in a 25 year old mother who developed B-cell lymphoma 2 1/2 years after the birth of her child [7].

Other neonatal complications reported include intrauterine growth retardation (4) hyperbilirubinemia (4), respiratory insufficiency requiring ventilatory assistance in 2 patients, retrolental hyperplasia and methadone withdrawal in one patient each. All children are said to be developing normally and no congenital abnormalities were reported.

Discussion

Transplantation has evolved as an accepted procedure for failed organs, but the long term effects of immunosuppression still remain a concern. Previous publications regarding pregnancy following renal transplantation [8 - 10], have reported complications such as congenital abnormalities, adrenocortical insufficiency, infections, liver dysfunction and seizures. These patients were immunosuppressed with azathioprine and steroids, at dosages higher than those used today. Only four patients received azathioprine as the main immunosuppressive agent. Although there were neonatal complications reported in one child [6], no long term sequelae were observed.

Cyclosporine has been shown to cross the placenta [11], and levels have been reported in the newborns born to mothers on CyA. Our report documents the use of this immunosuppressive agent in 18 patients who received liver transplantation without any significant adverse sequelae. FK506, the newest immunosuppressive agent was used in 3 patients, 2 of whom delivered babies. Both of these had a history of CyA use and received FK506 only for 2 weeks and 8 months prior to pregnancy. No valid conclusion can be drawn from the use of this agent in such short intervals of time.

The risk of rejection does not appear to be increased during pregnancy, with only one case of acute rejection diagnosed by biopsy. Despite enzyme elevations seen, those not treated immediately underwent resolution along with those that received treatment. 30% of the patients had increasing hepatic enzyme activity in the antepartum period with 45% having alterations in the post-partum period. Again, spontaneous resolution occurred in 50% of cases.

Overall, of 29 babies born to 22 liver transplant recipients, 60% of births occurred by cesarean delivery with a 88% incidence of prematurity seen in this group. Contributing factors were prelampsia,

premature rupture of membranes, and early fetal distress. Neonates born by NSVD sustained less maternal complications and were more normal in size, while 10% of babies delivered at full gestational age were small for gestational age. No congenital abnormalities were reported, and except for 3 infant deaths (10%), all others are reported to be alive and well. It is reasonable to assume that liver transplant recipients can still undergo a successful pregnancy, but it is not without risks. We suggest that careful monitoring be carried out by both a perinatologist and a transplant physician in order to minimize complications to both mother and child.

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