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CHILDBEARING AFTER LIVER TRANSPLANTATION,[1,2]

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Abstract

Seventeen female patients who underwent orthotopic liver transplantation between June 1973 and June 1987 became pregnant 5 months to 11 years after transplantation. Immunosuppression was maintained with combinations of prednisone, cyclosporine, and azathioprine prior to and during pregnancy. One patient discontinued immunosuppression after knowledge of pregnancy, taking only azathioprine sporadically. Mean age at time of delivery was 26 years. Twelve patients had no alteration in liver function studies; 7 patients demonstrated mild or moderate enzyme elevations prior to delivery, with one case of rejection confirmed by percutaneous liver biopsy. Major problems related to pregnancy were hypertension, anemia, and hyperbilirubinemia. Twenty live births occurred (2 patients had 2 separate pregnancies, one patient had a set of twins); 13 were by caesarian section, 7 by vaginal delivery. Eleven of the 13 caesarian births were premature by gestational age. All vaginal births were term. Toxemia of pregnancy and early rupture of membranes were the principal indications for caesarean section.

There were no congenital abnormalities or birth defects and all the children are surviving well. Fifteen of 16 children older than one year all have normal physical and mental development, with one child manifesting immature speech development. Four children are under one year, all with normal milestones thus far. Sixteen of the 17 mothers are alive from 2–18 years after transplantation; the only death was from a lymphoma, almost 4 years after transplantation and 2½ years after delivery. This experience suggests that women undergoing liver transplantation can safely bear children despite an increased risk of premature caesarian births. The effect of chronic immunosuppression of female pediatric patients on their reproductive potential later in adulthood remains to be fully evaluated but the results so far are favorable.

Liver transplantation (OLTx) has been performed successfully in the United States since 1967, with over 2000 transplants carried out at the University of Colorado and the University of Pittsburgh combined. Since the introduction of cyclosporine in 1980, improved long-term survival rates have been achieved. Subsequently, more patients are able to return to a relatively normal style of living. This near-normalcy has been accompanied by increasing desire to have children despite concern associated with the long-term use of immunosuppressive medications.

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Since the first successful pregnancy in a liver transplant recipient took place in 1976 (1,2), a total of 20 infants have been born to 17 liver transplant recipients who underwent surgery in the combined programs of the University of Colorado and the University of Pittsburgh. To the best of our knowledge, this is the first large series of patients who, after liver transplantation, have experienced childbirth.

We now report the results of these 20 births, which occurred between 1977 and 1988. The outcome and complications during pregnancy were assessed along with the alterations in hepatic function that occurred pre- and postdelivery.

MATERIALS AND METHODS

Patient population

Three patients underwent liver transplantation at the University of Colorado between 1973 and 1979, with the remaining 14 receiving transplants at the University of Pittsburgh during the period from 1983 to 1987. Table 1 summarizes the clinical history of these patients. Mean age of all patients was 25 years at time of pregnancy. Average time from transplantation to diagnosis of pregnancy was 26 months (range of 5 months to 11 years). The youngest patient, transplanted for biliary atresia at 4.5 years of age, subsequently became pregnant 11 years later. All other patients were adults at the time of liver transplantation.

All but one patient underwent a single liver transplantation, with one retransplantation occurring due to primary nonfunction of the initial graft. Immunosuppression consisted of azathioprine, prednisone and antilymphocyte globulin prior to 1980 and cyclosporine-prednisone after 1980. Azathioprine was added to the cyclosporine-prednisone regimen in only one patient prior to and during pregnancy. One patient discontinued immunosuppression at the time of diagnosis of pregnancy, which occurred nearly one year after her liver transplant. She now remains off all immunosuppression with normal liver function studies.

In the cyclosporine-steroid era, one patient received ALG and four received OKT3 for treatment of severe rejection in the initial 6 weeks following transplantation. None required retransplantation for rejection. Following discharge, all patients continued to be followed by physicians in Pittsburgh but were primarily managed by their initial referring physician and obstetrician.

Gynecological history

Except for one pediatric patient, all patients were within the childbearing years at the time of liver transplantation. Five patients had had children prior to their OLTx. One developed Budd-Chiari syndrome secondary to the use of medroxyprogestone acetate for infertility (1). This led to progressive liver failure requiring liver transplantation 2 years later. Following her transplant, ovulation was again induced by clomiphene citrate, resulting in a pregnancy 18 months after her OLTx. Two additional patients had difficulty maintaining pregnancies pre-OLTx. One clomiphene-induced pregnancy aborted in the first trimester; the other patient suffered 2 spontaneous abortions and one ectopic pregnancy before successfully having a full-term pregnancy. Both of these patients conceived within a year after OLTx.

There were three reported therapeutic abortions occurring in 2 patients after OLTx. Two were performed in a recipient after she had had a difficult premature delivery; the second patient later completed a second pregnancy. One spontaneous abortion occurred after OLTx. This patient became a mother twice within the next 3 years following her OLTx.

Pregnancy management

All recipients were classified as high-risk pregnancy patients and managed by both their obstetrician and the Pittsburgh group. Three patients required hospitalization and observation for at least one week prior to delivery. Only one patient was required to return to Pittsburgh for hospitalized management in the perinatal period.

RESULTS

From 1977 to 1988, 17 recipients of orthotopic liver transplantation gave birth to 20 infants, 1–12 years after their liver transplantation (mean 2.6 years). Mean age at the time of delivery was 26 years. The results of the pregnancies are listed in Table 2. There were 7 normal spontaneous vaginal deliveries (NSVD)* and 12 caesarean sections (1°CS) (one patient had a set of twins). All infants born by NSVD were full term (37%). Mean birth weight in this group was 2940 g. Only one patient who delivered by NSVD had toxemia precipitating delivery; all others were without complications.

Ten of the remaining 13 neonates delivered by 1°CS were premature by gestational age (83%). Mean birth weight was 1980 g, with a mean gestational age of 34 weeks. Three patients required 1°CS due to severe toxemia of pregnancy that occurred at 28, 32, and 35 weeks' gestation. The infant born at 28 weeks' gestation required ventilatory assistance for 7 days due to immaturity of the lungs. Premature rupture of membranes (PROM) precipitated early 1°CS in two patients at 28 and 35 weeks' gestation. Fetal distress and prolonged labor due to cephalopelvic disproportion, breech presentation, and transverse lie of the fetus each caused 1°CS. One set of twins, born at 34 weeks, sustained intrauterine growth retardation that necessitated 1°CS. Only one patient experienced severe discomfort in the area of the liver along with increasing liver enzymes abnormalities. This resulted in 1°CS performed at 32 weeks.

Liver function studies

Of 19 pregnancies, 12 were characterized by relatively stable liver function studies as reflected in the transaminases and bilirubin (Table 3). Some patients demonstrated mild-to-moderate elevations in alkaline phosphatase but this was attributed to normal pregnancy changes. Chronic rejection was the diagnosis made in one patient whose transaminases were elevated at the beginning of pregnancy. This patient continued to sustain ongoing injury and progressive hyperbilirubinemia throughout her pregnancy. There were four cases of mildly elevated liver function tests, with the bilirubin more significantly elevated than the rise in transaminase. All were followed closely and required no treatment up until time of delivery.

Moderate elevations in liver functions were seen in three patients. One underwent a liver biopsy demonstrating acute rejection along with areas of hepatitis. This patient had treatment deferred until after delivery one week later. Partial resolution of the elevated liver enzymes occurred before treatment was undertaken. Another patient, with a diagnosis of recurrent hepatitis B prior to pregnancy, underwent a liver biopsy 2 months before delivery. This was reported as mild hepatitis. No rejection was seen. The third patient, who had a biopsy at the beginning of pregnancy, was reported to have chronic rejection. Further workup for progressive enzyme elevation was deferred until the postpartum period.

Significant changes in hepatic function were brought about by delivery of the newborn. Nine cases showed no significant change in liver enzymes within eight weeks postpartum.

*Abbreviations CS, caesarian section; NSVD, normal spontaneous vaginal delivery; PROM, premature rupture of membranes; PTC, percutaneous transhepatic chalangiography.

Similarly, 10 cases of persistent abnormalities in hepatic function were recorded (Table 3). Three resolved spontaneously without any intervention. One with known hepatitis B had another biopsy at 2 months postpartum that revealed ongoing hepatitis. Minimal-to-mild rejection also noted was not treated. An additional four patients were given a steroid bolus for treatment of enzyme abnormalities seen from 2 to 8 weeks postpartum. One patient showed an immediate improvement in hepatic function. Three remained unchanged initially, but spontaneous resolution occurred within 4 weeks. None of these patients had a liver biopsy performed for definite diagnosis. Percutaneous transhepatic cholangiography (PTC) was performed on three additional patients for enzyme elevations postpartum. Two had simultaneous biopsies that revealed no rejection: one was normal, the other consistent with cell swelling and vacuolization. Both PTCs demonstrated normal biliary duct architecture. The third patient, presumed to have chronic rejection on a previous biopsy, demonstrated multiple duct strictures and abscesses on PTC. Several drainage procedures were required, followed by retransplantation 2 months later. Thrombosis of the donor hepatic artery was revealed at surgery, a finding not detected on earlier sonographic evaluations.

Immunosuppression

Except for one patient who voluntarily discontinued her medication, all other patients remained on standard therapy, as before pregnancy. Two received azathioprine and prednisone; thirteen took CsA and prednisone. None had significant changes in dosages. One patient received triple therapy during the course of her pregnancy. Five patients required a decrease in dosages of CsA primarily in the last trimester. Three were decreased because of elevated CsA blood levels; one, for deterioration in renal function. The fifth patient's dosage was decreased because of persistent hepatitis on liver biopsy. The dose of prednisone remained the same throughout the pregnancy course in all patients.

Complications

Six cases were complicated by hypertension requiring treatment. Four of these had associated toxemia of pregnancy requiring 1°CS for early delivery. Anemia was also a significant problem in six others, two of whom required blood transfusions in midpregnancy. Hyperbilirubinemia was also seen in six cases, as discussed earlier, with this manifestation also associated with elevated transaminases. Single cases each of urinary tract infection with stones, adrenal insufficiency, and endometritis were reported as maternal complications. Among the neonates, intrauterine growth retardation was seen in 4 infants, including one set of twins; birth weight averaged 1400 g. Although small for gestational age, none required ventilatory assistance. Respiratory insufficiency was noted in one infant born at 28 weeks gestation, as a result of toxemia in the mother. In addition to hyaline membrane disease, this infant suffered both apneic and bradycardiac episodes, as well as hyperbilirubinemia due to neonatal jaundice. Abnormality of speech development was noted in this child at age 2.5 years. One additional infant suffered also from neonatal jaundice but this resolved without sequelae. Another infant, born to a mother on methadone (and $HbsAg^{+}$), sustained methadone-withdrawal symptoms.

There were no reported cases of congenital abnormalities or birth defects. With the exception of immature speech development in one child, all others continue to grow and demonstrate normal development. Ages presently range from 9 months to 12 years. Fifteen children are still under 3 years of age but all have a normal developmental pattern. No cases of adrenocortical insufficiency or lymphopenia were reported in this series of infants.

One child born to a mother with Wilson's disease has been found to be a heterozygote for the gene, with normal serum copper and urinary excretion of copper. This child is presently 7 years of age with normal liver function studies. One infant, born to a mother with hepatitis

B, showed no liver dysfunction or coagulopathy. She was immediately vaccinated and is now doing well at 10 months.

Present maternal survival

Sixteen of the 17 mothers are alive from 2 to 18 years after transplantation. The seventeenth recipient was a 25-year-old woman (patient 9) who delivered a normal baby 16½ months after transplantation, and died of a B cell lymphoma 2½ years later.

DISCUSSION

Liver transplantation has been performed for more than two decades. Approximately 11% of those transplanted have been female patients in their childbearing years who have expressed increasing desire to resume a normal family life. Within the last 5 years, there has been a larger population of pediatric patients coming to liver transplantation, representing nearly 30% of all patients transplanted, and having a greater than 70% chance of survival into and beyond the reproductive years. The reproductive potential of these patients is of significant concern to those involved. Previously reported cases of pregnancy following liver transplantation have been isolated case reports (1,3). Much more has been written about pregnancy following renal transplantation, including a comprehensive report of 17 pregnancies from the University of Minnesota (4) and 64 pregnancies caused by both male and female renal recipients from the University of Colorado (5). Many more complications to the mother and the newborn were reported, including one death and the development of carcinoma in two patients. Penn et a1. (5) reported a 49% rate of prematurity and a 30% complication rate among newborns of female kidney recipients, including respiratory distress, congenital abnormalities, adrenocortical insufficiency, infection, liver dysfunction, and seizures.

Our report of 20 live births from 17 recipients of liver transplantation is the largest series so far. From our experience there has been no increased risk due to the physical presence of the fetus. Although 11/18 (60%) pregnancies were unplanned, there were only three additional pregnancies that were terminated in 2 of our mothers for nonmedical reasons, but both patients subsequently delivered live babies.

Medically, the major concern to the mother was the potential loss of graft function. Although the incidence of elevated hepatic enzymes was 35% during the course of the pregnancy, there was only one documented case of acute rejection with hepatitis occurring in the third trimester. Resolution was seen even before treatment was initiated and upon delivery of the fetus. However, the abnormalities in hepatic function associated with the delivery process were in most cases not consistent with rejection. Those that were treated blindly had only a 25% response to steroids. Greater than 80% of those not treated resolved spontaneously, with 2 undergoing biopsies that revealed no rejection. Therefore the progressive elevation in liver function seen after delivery did not correlate with rejection.

One of the most significant findings was the 63% incidence of caesarian sections. Among this group was an 83% prematurity rate with a mean gestational age of 34 weeks. The main cases of 1°CS included toxemia and premature rupture of membranes. Despite the larger number of premature babies (55% overall), only one infant had respiratory insufficiency due to hyaline membrane disease, which required intubation for seven days. The risk of prednisone therapy to the fetus may be associated with respiratory distress, lymphopenia, and adrenocortical insufficiency. These effects were not manifested in the offspring of our patients, and there were no infectious complications in the infants as a result of exposure to chronic immunosuppression.

One patient, concerned about the long-term effects of immunosuppression, chose to discontinue her therapy during her pregnancy. Fortunately this patient suffered no sequelae and is still maintaining normal liver function now 7 years later. The effect of azathioprine on offspring is of great concern since it has been shown to produce congenital abnormalities and chromosomal aberrations in experimental animals (6,7). However, three of our patients were immunosuppressed with azathioprine during their pregnancies, with one patient having 2 separate pregnancies. All children are without obvious effects of the immunosuppression.

There was a single case in which ALG was used and 5 cases with OKT3 in patients prior to pregnancy. The long-term effects of these medications is unknown. Cyclosporine, known to pass transplacentally, has not shown any adverse effects in neonates born to mothers chronically immunosuppressed with this drug. Tests conducted by Sandoz, Inc., have not shown CsA to be mutagenic and cyclosporine has not been shown to produce chromosomal abnormalities in animals. There were also no reported septic complications in the neonates as a result of this chronic exposure, and no obvious long-term complications were noted. Two patients who delivered their babies in Pittsburgh underwent measurements of CsA metabolites in cord, placenta, and maternal blood (8). It appeared that a very high concentration of metabolites occurred in the placenta and umbilical cord, concentrations nearly 10–20 times that seen in maternal blood. Burrows et a1. (9) reported cord blood levels of CsA that were 34% and 57% of maternal CsA levels found at delivery in twins born to a mother on CsA and prednisone. These babies were delivered at 35 weeks' gestation as a result of preeclampsia.

In summary, 17 patients following liver transplantation have given birth successfully to 20 healthy children, despite chronic immunosuppression. Three children were born to mothers on azathioprine and steroids, all with full-term and vaginal deliveries. Sixteen children were exposed to cyclosporine and steroids, with known passage of this immunosuppressant across the placenta. Coincidentally, a larger percentage of these infants was premature (68%) and small for gestational size. Despite the increased risk of prematurity and increased number of caesarian births, our experience suggests that liver transplantation is not a contraindication to bearing children. The effect of chronic immunosuppression on pediatric recipients of liver transplantation and the subsequent danger to alterations in their reproductive capacity later in adulthood has yet to be evaluated, but the prospects remain favorable.

Addendum

Information regarding an 18th patient and subsequent birth of 2 children was obtained after completion of this article. This patient underwent her OLT in Denver, Colorado at the age of 23 for chronic active hepatitis, and was delivered of her first baby 7 years later. The child was born prematurely around 30 weeks gestation, and weighed 1100 g. Immediately following delivery, the mother required emergency laparotomy for small bowel obstruction secondary to internal herniation of jejunum through the mesentery of her Roux-en-Y loop. The baby required two operative procedures: the first for correction of a cardiac abnormality and the second to prevent detachment of her retina (specific details not obtained). Mother and child subsequently did well, and the baby was discharged at 3 months. No hepatic enzyme abnormalities were reported during this pregnancy.

Three and a half years later, the patient was delivered of a second child, noted to be small for gestational age. Workup for failure-to-thrive revealed the baby, and subsequently the mother, to be positive for the human immunodeficiency virus. The child, now 6 months of age, is doing poorly and the mother unfortunately died of complications secondary to her HIV infection, 11½ years after liver transplantation.

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Table 1

Clinical information about patients

Patient No.	Pregnancy No.	Age at Pregnancy (years)	Diagnosis at OLTx[a]	Interval from OLTx to Pregnancy (months)	Parity Pre-OLTx
1	1	16	Biliary atresia	138	Premenarche
2	2	26	Budd-Chiari syndrome	18	PoGo
2	3	28		48	
3	4	23	Wilson's Disease	11	$P_1G_0Ab_1$
4	5	27	Chronic active hepatitis	11	$P_4G_1Ab_3$
5	6	30	Sclerosing cholangitis	36	P_1G_1
6	7	33	Chronic active hepatitis	12	P_0G_0
7	8	29	Cryptogenic cirrhosis	22	P_0G_0
7	9	31		32	—
8	10	23	Chronic active hepatitis	22	P_1G_1
9	11	25	Chronic active hepatitis	7	$P_1G_0Ab_1$
10	12	19	Chronic active hepatitis	12	P_0G_0
11	13	27	Secondary biliary cirrhosis	6	P_2G_2
12	14	25	Chronic active hepatitis	8	P_0G_0
13	15	31	Primary biliary cirrhosis	18	P_0G_0
14	16	23	Acute hepatic failure	22*	P_1G_1
14	17	—	—	22	—
15	18	22	Sclerosing cholangitis	5	P_1G_1
16	19	20	Alpha-1-antitrypsin deficiency	6	P_0G_0
17	20	33	Chronic active hepatitis	12	$P_1G_0Ab_1$

[a] OLTx: Orthotopic liver transplantation.

[b] Patient delivered twins.

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Table 2

Results of childbirth in 17 female liver transplant recipients

Patient No.	Pregnancy No.	Gestational Age (weeks)	Type of delivery	APGAR score	Sex	Weight (g)	Complications
1	1	39	NSVD[a]	9	F	3660	None
2	2	40	NSVD	9	M	2400	None
	3	41	NSVD	9	F	2550	None
3	4	40	NSVD	9	F	3150	None
4	5	28	1° CS	8	M	1220	Toxemia, respiratory insufficiency
5	6	35	1° CS	9	F	2400	Premature ROM
6	7	38	1° CS	9	M	3090	Transverse lie
7	8	34	1° CS	9	M	1590	Fetal distress, anemia, hypertension in mother
7	9	39	1° CS	9	M	2020	None
8	10	38	NSVD	7	F	3050	Anemia
9	11	38	NSVD	9	F	2550	None
10	12	32	1° CS	9	M	2100	Discomfort and enzyme abnormality of liver
11	13	38	NSVD	–	M	3210	Toxemia and anemia
12	14	36	1° CS	3	M	1690	Toxemia, anemia, intrauterine growth retardation
13	15	35	1° CS	8	M	2870	Toxemia, anemia
14	16	34[b]	1° CS	9	M	1020	Anemia, HTN, intrauterine growth retardation
14	17	34[b]	(Twins)	8	M	1330	Anemia, HTN, intrauterine growth retardation
15	18	28	1° CS	9	F	1450	Premature ROM
16	19	35	1° CS	9	M	2500	Prolonged labor
17	20	35	1° CS	–	F	2330	Breech presentation

[a] CS, caesarian section NSVD: normal spontaneous vaginal delivery; ROM: rupture of membranes; HTN: hypertension.

[b] Twins.

Table 3

Alterations in liver function teats seen during 19 pregnancies after OLTx

Alterations in tests	No. Patients
Anterpartum period	
Stable LFTs[a]	12
Mild elevations in LFTs	4
Moderate elevations in LFTs	3
Postpartum period	
Stable LFTs	9
Moderate elevation in LFTs	10
Spontaneously resolved	3
Treated with steroid bolus	4
PTC and liver biopsy done	3

[a]LFT: liver function test; PTC: percutaneous transhepatic cholangiogram.