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 caesarean section, 7 by vaginal delivery. Eleven of the 13 caesarean 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 2 1/2 years after delivery. This experience suggests that women undergoing liver transplantation can safely bear children despite an increased risk of premature caesarean 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.

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 1978, 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 antithymocyte 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 on 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 Badd-Chiari syndrome secondary to the use of medroxyprogesterone acetate for infertility (J). 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's 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's 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's 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's 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's CS. One set of twins, born at 34 weeks, sustained intrauterine growth retardation that necessitated 1's CS. Only one patient experienced severe discomfort in the area of the liver along with increasing liver enzymes abnormalities. This resulted in 1's 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.

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**Table 1. Clinical information about patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Pregnancy No.</th>
<th>Age at Pregnancy (years)</th>
<th>Diagnosis at OLTx*</th>
<th>Interval from OLTx to Pregnancy (months)</th>
<th>Parity Pre-OLTx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>16</td>
<td>Biliary strasis</td>
<td>138</td>
<td>Premenarche</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>25</td>
<td>Budd-Chiari syndrome</td>
<td>18</td>
<td>PbCo</td>
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<tr>
<td>3</td>
<td>3</td>
<td>28</td>
<td>Wilson's Disease</td>
<td>11</td>
<td>P,G,A,Ab</td>
</tr>
<tr>
<td>4</td>
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<td>27</td>
<td>Chronic active hepatitis</td>
<td>11</td>
<td>P,G,A,Ab</td>
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<tr>
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<td>30</td>
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<td>Cryptogenic cirrhosis</td>
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<td>P,G</td>
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<td>—</td>
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<td>Chronic active hepatitis</td>
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<td>20</td>
<td>Chronic active hepatitis</td>
<td>12</td>
<td>P,G,A,Ab</td>
</tr>
</tbody>
</table>

* OLTx: Orthotopic liver transplantation.

* Patient delivered twins.
Simultaneous biopsies that revealed no rejection: one was for enzyme abnormalities seen from 2 to 8 weeks postpartum. A liver biopsy performed for definite diagnosis. Three remained unchanged initially, but spontaneous change in liver enzymes within eight weeks postpartum.

One patient showed an immediate improvement in hepatic function. Additional four patients 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 azathoprine 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 1st 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
Development was noted in this child at age 2.5 years. The infant suffered from neonatal jaundice but was discharged without sequelae. Another infant, born to a mother with Wilson's disease (and HbsAg+), sustained methadone-withdrawal syndrome but showed no liver dysfunction or lymphopenia. She was immediately vaccinated and is now healthy.

No reported cases of congenital abnormalities or infections. With the exception of immature speech development, all children continue to grow and develop normally. Ages presently range from 9 months to 18 years. No cases of adrenocortical insufficiency or lymphopenia were reported in this series.

One 18-month-old child with Wilson's disease has been a heterozygote for the gene, with normal serum copper excretion of copper. This child is presently at risk of normal liver function studies. One infant, born to a mother with hepatitis B, showed no liver dysfunction or lymphopenia. She was immediately vaccinated and is now healthy.

Maternal survival. Sixteen of the 17 mothers are alive 18 years after transplantation. The seventeenth, a 25-year-old woman (patient 9) who delivered a boy by cesarean section 16 months after transplantation, and died of a heart attack 24 years later.

DISCUSSION

Transplantation has been performed for more than two years. Approximately 11% of the transplanted children have been pregnant in their childbearing years who have experienced desire to resume a normal family life. Within the University of Minnesota (4) transplant program, 31 cases of pregnancy in children transplanted, representing nearly half the patients transplanted, and having a greater than 90% survival rate at the time of delivery and beyond the reproductive years.

The potential of these patients is of significant concern. Previously reported cases of preg- nancy in children transplanted have been isolated cases. More has been written about pregnancy in children transplanted, including a comprehensive review of pregnancies from the University of Minnesota (4) and cases at the University of Colorado (5). Many more cases have been reported, with the development of carcinoma in two pregnancies from this series (5). A single case in which ALG was used and 5 cases of maternal transplantation in 20 infants 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 of maternal transplantation 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 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.

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 jejumum through the mesentry 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 other, 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.

REFERENCES


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IMPROVED RESULTS USING OKT3 AS INDUCTION IMMUNOSUPPRESSION IN RENAL ALLOGRAFT RECIPIENTS WITH DELAYED GRAFT FUNCTION1,2

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Delayed graft function remains a major problem in cadaveric renal allograft transplantation. We have used different immunosuppressive induction regimens in patients with delayed graft function. The first regimen,

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Department of Surgery.
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used in 40 patients from January 1985 to December 1986, consisted of CsA (8 mg/kg/day, orally within 48 hr of cadaveric renal transplantation regardless of graft function), azathioprine (1.5–2.5 mg/kg/day), and steroids (methylprednisolone 375 mg on day 0, then prednisone tapered to 30 mg/day by day 10 with slow tapering to 7.5–10 mg/day over the first 6 months after transplantation). A second regimen, used from January 1987 to March 1989, employed the same doses of azathioprine and steroids; however, OKT3 (5 mg i.v./day for 7–21 days) was administered in the 34 patients who had delayed graft function. CsA was withheld until ATN resolved.

The use of OKT3 as induction immunosuppression in