Pregnancy Outcome in Female Liver Transplant Recipients


ABSTRACT

Transplantation has become an available and successful treatment option for numerous congenital and acquired hepatic disorders. Studies have shown that when the prepregnancy recipient graft function is stable and adequate, pregnancy is normally well tolerated with favorable neonatal outcomes. However, there are reports of increased incidences of hypertension and preeclampsia as well as lower birth weights and prematurity. Patients administered tacrolimus-based therapies seem to have lower incidences of these complications.

Case Reports. The 5 reported patients, aged 23–37 years at the time of conception, were 2–11 years posttransplantation. A preterm delivery for fetal distress was the most clinically important complication among these patients. One episode of acute genital herpes infection, 1 liver hematoma in a patient who was anticoagulated owing to a history of deep vein thrombosis, and 1 case of wound infection postpartum were also observed. Despite these complications, all 5 pregnancies were successful. The mean gestational age at delivery was 35.2 weeks. No structural malformations or early complications were observed in the neonates. All cases showed stable liver parameters.

Studies show that there are some differences in the complications profile depending on the immunosuppressive regimen prescribed. Transplant recipients administered tacrolimus-based therapies seem to have lower incidence of hypertension, preeclampsia, and infection, but a greater incidence of insulin-treated diabetes during pregnancy.

We have described 5 cases of pregnancy among women who had liver transplantation managed from 1991 to 2010.

CASE REPORTS

The State University of Campinas (Unicamp) in Brazil has a multidisciplinary and skilled staff trained to assist all high-risk pregnancies at a specialized outpatient prenatal care unit. For patients who undergo transplantation, an integrated follow-up involving obstetric care and a liver transplant team are required to achieve maternal and fetal well-being.

Since 1991, a total of 500 liver transplants have been performed; 162 were women and 34 were of reproductive age. We are reporting on 5/34 of pregnancy among these patients. From January 1991 to October, 2010, there were a total of 32,836 deliveries at the maternity unit, which correspond with a very low...
0.015% rate of pregnancy after liver transplantation among all childbirths.

CASE REPORTS

Patient 1
A 26-year-old primipara was transplanted in 1991 due to Budd-Chiari syndrome 4 years before this pregnancy, using cyclosporine and prednisone 7.5 mg/d. This patient was also being treated for a hypertensive disorder with propranolol and submitted to anticoagulation therapy after deep venous thrombosis. Pregnancy was diagnosed around 13 weeks of amenorrhea. At that time, the anticoagulation regimen was exchanged for low-molecular-weight heparin (maintaining an international normalized ratio [INR] of 2.5).

At 26 weeks of pregnancy, the patient was admitted for nausea and abdominal pain. Her laboratory examinations showed negative investigation for infectious disease, such as HIV, hepatitis, cytomegalovirus (CMV), toxoplasmosis, or rubella, and a hemoglobin level of 10.1 mg/dL. Normal liver and renal function were confirmed. During this hospitalization, endoscopy was performed and showed esophageal varices of thin caliber and mild gastritis. Obstetrical ultrasound showed no abnormalities, with normal Doppler of the umbilical artery, but abdominal imaging revealed an enlarged spleen (219 × 71 mm) and an ecogenic image in her hepatic right lobe, with 63 × 31 × 19 mm interpreted as an hematoma. At this point, the patient’s hemoglobin level had dropped to 8.4 mg/dL; however, she was clinically stable, and had orientation for bedrest and ambulatory evaluation once a week.

At 30 weeks and 4 days of the pregnancy, the patient was again hospitalized for a blood transfusion (hemoglobin level, 7.5 mg/dL) and fetal well-being evaluation with normal Doppler ultrasound and fetal biophysical profile of 8. At 33 weeks and 6 days of the pregnancy, the patient was admitted for an emergency Cesarean section for fetal distress, giving birth to a preterm newborn weighing 1,407 g, an Apgar score of 9/9 and postnatal assessment of gestational age (Capurro’s method) of 39 weeks and 2 days. At that time, a tubal ligation was performed through a periumbilical incision.

Patient 2
A 31-year-old primiparous woman was transplanted for autoimmune hepatitis 2 years before this pregnancy; immunosuppression consisted of 4 mg tacrolimus and 5 mg prednisone per day. This patient had normal renal and liver function before conception and maintained stable laboratory controls through the whole gestational period with no complications or need for hospital admission.

At 36 weeks and 5 days, the patient was admitted in labor and submitted to an instrumental vaginal delivery, under epidural analgesia, yielding a healthy, low-weight (2430 g) newborn with an Apgar score of 9/9 and postnatal assessment of gestational age (Capurro’s method) of 39 weeks and 2 days. At that time, breastfeeding was contraindicated because of the immunosuppressive regimen and the patient maintained normal renal and liver function during the postpartum period.

Patient 3
A 23-year-old primipara was transplanted due to autoimmune hepatitis 6 years before this pregnancy; immunosuppression consisted of taking 4.0 mg of tacrolimus per day and 7.5 mg of prednisone. This patient had normal renal and liver function before conception and maintained stable laboratory controls through the whole gestational period with no complications or need for hospital admission.

At 36 weeks and 5 days, the patient was admitted in labor and submitted to an instrumental vaginal delivery, under epidural analgesia, yielding a healthy, low-weight (2430 g) newborn with an Apgar score of 9/9 and postnatal assessment of gestational age (Capurro’s method) of 39 weeks and 2 days. At that time, a tubal ligation was performed through a periumbilical incision.

Patient 4
A 37-year-old woman was transplanted due to autoimmune hepatitis 9 years before this pregnancy; immunosuppression consisted of 2.0 mg of tacrolimus per day and with normal renal and liver function before conception. The patient had a background of 1 first trimester abortion 5 years posttransplant. During the first ultrasound examination at 12 weeks of gestation, a diagnosis of cystic hygroma was made; no other abnormalities were noticed, with normal cariotype and negative investigation for intrauterine infections, such as toxoplasmosis, rubella, CMV, and syphilis.

At around 28 weeks of pregnancy, the patient had a cutaneous erythema with vesicles on her abdomen and lower back with the diagnosis of Herpes zoster, treated with acyclovir for 10 days. At 39 weeks of pregnancy the patient was admitted for spontaneous rupture of membranes and a Cesarean section was performed due to active genital herpes infection. A healthy, 3000-g baby, Apgar score 9/10 and postnatal assessment of gestational age (Capurro’s method) of 38 weeks and 3 days, was delivered. A barrier method was indicated for contraception.

Patient 5
A 23-year-old primipara was transplanted due to autoimmune hepatitis 11 years before this pregnancy; immunosuppression consisted of 5 mg of tacrolimus per day. This patient had normal renal and liver function before conception and maintained stable laboratory controls throughout the gestational period.

At around 32 weeks of pregnancy, this patient was admitted for preterm labor. Corticosteroids had already been administered for fetal lung maturation and inhibition was not tried (the patient was initially 5 cm dilated). However, a Cesarean section was performed due to functional dystocia. A healthy, 1900-g baby, Apgar score 8/10 and postnatal assessment of gestational age (Capurro’s method) of 32 weeks and 3 days, was delivered, with good evolution after hospital discharge (Table 1).

Immediately postpartum, the patient required a blood transfusion, but recovered very well and was discharged 72 hours later. Seven days after delivery, the patient was again admitted, this time for an infected hematoma and urinary tract infection. Intravenous antibiotics were prescribed and a surgical procedure necessary. After 4 days she was again discharged with no additional complications. An intrauterine device (IUD) was indicated as contraceptive advice.

In all patients, breastfeeding was contraindicated because of the immunosuppressive regimen and the patient maintained normal renal and liver function during the postpartum period.

DISCUSSION
Over the last 2 decades, obstetricians have faced different kinds of challenges due to medical evolution and the development of possible treatments for various critical
clinical and surgical conditions. Considering the history of hepatic insufficiency and transplantation, about 20 years ago it would have been impossible to predict the association between transplanted patients, immunosuppressive therapy, durability of grafts, and a normal gestation. However, the number of successful cases of transplantation has increased enormously with improvements in surgical techniques and safer immunosuppressive regimens, which have brought a new life perspective to these patients.4-11

According to the literature review, the main cause of loss of hepatic function in young women is autoimmune hepatitis,5-7 which was the disease involved in 3 of these 4 cases.

Reproductive-age women are able to reestablish ovulation after transplantation and contraception has become an important part of medical counseling. Not only that, but the discussion of which of these patients could plan a gestation and what would be necessary during prenatal care is also possible.

Transplanted patients with lower risk during pregnancy are those who become pregnant >2 years posttransplantation, have stable and normal hepatic function, have normal renal function, and whose immunosuppressive therapy is in maintenance dosage.6 It is also important to know the blood type and investigate the serologic status for hepatitis B and C, HIV, toxoplasmosis, rubella, and CMV for each patient.

The ideal condition would be to perform laboratory investigations and promote a psychological evaluation to indicate the possibility of pregnancy, with the knowledge that a specialized prenatal care is necessary with a multidisciplinary team for follow-up, involving not only the routine examination, but a rigorous fetal well-being control, ultrasonography for morphologic and growth assessments, hepatic and renal function, potassium dosages, and monthly CMV antigenemia testing.

The immunosuppressive therapy used in the cases reported herein were cyclosporin and tacrolimus, with or without prednisone, which are considered safe during pregnancy; both are class C medications in the latest drug and pregnancy recommendation document.7 However, there is a reported increased risk of intrauterine growth restriction, hypertensive disorders, and prematurity.8 Among the cases currently reported, only 1 case of preterm birth was recorded. Breastfeeding should be discussed in an individual basis, considering the immunosuppressive regimen used.6-10

Increasing experience with management of transplanted patients, pregnancy complications, labor, and neonates have allowed coordinated care and close surveillance for pregnant women who have undergone transplantation, with a high number of successful cases worldwide.10,11 The possibility of follow-up with frequent blood chemistry tests, serial ultrasound, and infection screening can assess risk factors, associated disease, and, therefore, predict complications as well as allow a quick introduction of treatment, when necessary.

REFERENCES


Table 1. Results of Pregnancy in Five Liver Transplant Recipients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Maternal Age (y)</th>
<th>Liver Disease</th>
<th>Years After Transplant</th>
<th>Immunosuppressive Therapy</th>
<th>Outcomes</th>
<th>Maternal Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>Budd–Chiari syndrome</td>
<td>4</td>
<td>Cyclosporine, prednisone</td>
<td>C-section; 1270 g; Apgar score; 1/2/8</td>
<td>Hepatic hematome</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>Autoimmune hepatitis</td>
<td>2</td>
<td>Tacrolimus, prednisone</td>
<td>C-section; 3465 g; Apgar score, 8/9</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>Autoimmune hepatitis</td>
<td>5</td>
<td>Tacrolimus, prednisone</td>
<td>Vaginal delivery; 2430 g; Apgar score, 9/9</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>Autoimmune hepatitis</td>
<td>8</td>
<td>Tacrolimus</td>
<td>C-section; 3000 g; Apgar score, 9/10</td>
<td>Herpes zoster</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>Autoimmune hepatitis</td>
<td>11</td>
<td>Tacrolimus</td>
<td>C-section; 1990 g; Apgar score, 8/10</td>
<td>Wound infection</td>
</tr>
</tbody>
</table>

Abbreviation: C-section, cesarean section.