Medical Management of the Liver Transplant Patient

Anne Burke

Graft 2003; 6; 136
DOI: 10.1177/1522162803256722

Medical Management of the Liver Transplant Patient

Anne Burke, MD
University of Pennsylvania Health Systems

The medical consequences of long-term immunosuppression are far-reaching. They include systemic hypertension, hyperlipidemia, diabetes mellitus, obesity, renal insufficiency, infection, osteoporosis, osteopenia, and malignancy. Systemic hypertension is managed by drug therapy, weight loss, and sodium restriction. Calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, and diuretics may be used. Diabetes mellitus occurs in 20% to 30% of liver transplant recipients. Renal insufficiency is common and often precedes transplantation. Serum creatinine concentrations > 1.6 mg/dl are found in more than 75% of liver transplant recipients after 3 years of follow-up. Treatment of renal insufficiency includes minimizing calcineurin inhibitors, avoiding other nephrotoxic drugs, control of hypertension, and control of diabetes mellitus. With regard to osteoporosis and osteopenia, bone turnover is greatly increased after transplantation due to excessive osteoclastic activity. Bone loss increases rapidly in the first 3 months after transplantation. Atraumatic vertebral fractures have been reported in up to 30% of patients within 6 months posttransplant. Treatment is based on z-scores. Morbidity includes insomnia, lassitude, cosmetic concerns, musculoskeletal pain, seizures, headache, and fine tremor. In females of child-bearing age, conception and pregnancy must also be managed.

Keywords: liver transplantation; systemic hypertension; renal insufficiency

The 10-year survival rate after liver transplantation is approximately 65%. With increasing numbers of long-term liver transplant survivors has come an appreciation of some of the health problems facing these patients. This article will focus on the long-term management of the liver transplant recipient with emphasis on general health concerns and routine health care maintenance.

Long-Term Morbidity and Mortality of Liver Transplantation

The main causes of late death after liver transplantation are shown in Table 1.

Liver transplant patients also have an increased prevalence of many chronic conditions that have a significant impact on quality of life (see Table 2), and these conditions frequently occur at a younger age than in the general population.

Medical Consequences of Immunosuppression

Cardiovascular Disease

There is an excess mortality from cardiovascular disease in liver transplant recipients (see Table 1). This is due to a combination of factors: hyperlipidemia, diabetes mellitus, hypertension, cigarette smoking, and obesity/sedentary lifestyle. In addition, oxidative stress and hyperhomocysteinemia may contribute to the risk.

Anne Burke, MD
Assistant Professor of Medicine
Division of Gastroenterology
University of Pennsylvania Health System
Philadelphia, PA
Tel: 215.898.9006
Fax: 215.349.5915
e-mail: aburke@mail.med.upenn.edu

DOI: 10.1177/1522162803256722

Table 1 | **Cause of Death in Liver Transplant Recipients after the First Year**

Cause of Death	Percentage of All Causes of Death
Graft failure	40
CVD	18
Infection	15
De novo malignancy	8
Other	19

Adapted from Abbasouglu et al. (1997).

Table 2 | **Causes of Morbidity in Liver Transplant Recipients after the First Year (not age-adjusted)**

Disease	Prevalence Posttransplant	Rate in U.S. Population
Hypertension (BP > 140/90)	41%-81%	15.7%
Hypercholesterolemia (> 240 mg%)	20%-66%	14.9%
HDL < 35 mg%	52%	12%
Diabetes mellitus	21%-32%	3.7%
Obesity (BMI > 30)	39%-43%	16.1%
Skin cancer (BCC and SCC)	10%	0.3%
Other cancers	2%	0.4%
Renal impairment	77%-80%	4%
Symptomatic fractures	10%	.04%

Cardiovascular Risk Factors

Many of the adverse health effects seen in liver transplant recipients are direct or indirect consequences of immunosuppression.

Systemic Hypertension

Epidemiology: Systemic hypertension is defined as diastolic pressure > 90 mmHg or systolic pressure > 140 mmHg. Systemic hypertension occurs in 40% to 80% of liver transplant recipients. It typically occurs within a few weeks of transplantation and is largely due to the use of calcineurin inhibitors.

Pathogenesis: The molecular mechanism underlying calcineurin inhibitor–induced hypertension is not fully understood, but renal vasoconstriction is the predominant abnormality seen. Corticosteroids add to the risk of hypertension. A history of hypertension prior to the development of liver disease is an important additional risk factor.

Clinical Management:

- Drug therapy: Drug therapy should be introduced early
- Weight loss: Patients should be encouraged to lose weight if more than 15% above their ideal body weight
- Sodium restriction: patients should be advised to restrict sodium intake to 2-4 g per day
- Other measures: stop smoking and reduce alcohol intake and increase exercise

Choice of drugs:

- Calcium channel blockers
  - Nifedipine and drugs of a similar class are preferred. Nifedipine is associated with development of peripheral edema.
  - Verapamil and diltiazem may inhibit cyp 450 drug metabolism of calcineurin inhibitors, and levels should be monitored
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (ATII) antagonists may also be used. ACE inhibitors and ATII antagonists may confer additional benefit by preventing left ventricular hypertrophy, a risk factor for cardiovascular disease. Initial concerns regarding worsening of renal function seem

SYSTEMIC HYPERTENSION

Systolic pressure > 140 mmHg and diastolic pressure > 90 mmHg

unfounded, and these drugs are as effective and as well tolerated as calcium channel blockers. Patients should be monitored for hyperkalemia and hypomagnesemia.

- Other drugs: Diuretics should be used to control peripheral edema or as second-line antihypertensives. The centrally acting sympatholytics such as clonidine are considered third-line agents against posttransplant hypertension.

Hyperlipidemia

Epidemiology: See Table 1. Sirolimus causes a dose-dependant increase in triglycerides rather than in cholesterol.

Pathogenesis: The mechanism whereby serum cholesterol levels are increased after liver transplantation is unclear.

Clinical Management:

- Review immunosuppression
- Dietary modification: rarely successful in isolation in the postliver transplant setting
- HMG CoA-reductase inhibitors ("statins")

OBESITY

> 20% above ideal body weight

Diabetes Mellitus

Diabetes mellitus is seen in 20% to 30% of liver transplant recipients. This arises from a combination of preliver transplant diabetes (13% in one study) and true postliver transplant diabetes. This compares to less than 4% in the general population.

Pathogenesis:

- Corticosteroids increase insulin resistance.
- Calcineurin inhibitors: The calcineurin inhibitors increase insulin resistance, injure pancreatic islet cells, and impair insulin secretion. Tacrolimus and cyclosporin are associated with an increased incidence of diabetes. The effect may be transient.

Chronic hepatitis C infection may potentiate the risk or severity of diabetes mellitus.

Clinical Management:

- General: Diabetic liver allograft recipients should be managed in the same way as diabetic patients in the general population, with lifestyle modification and drug therapy as needed.
- Modification of immunosuppressive protocol: Where possible, corticosteroids should be withdrawn and calcineurin inhibitor dose minimized. A conversion from tacrolimus to cyclosporin, sirolimus, or mycophenolate mofetil may be of help.

RENAL INSUFFICIENCY

Serum creatinine > 1.6 mg/dl in more than 75% of liver transplant recipients after 3 years follow-up

Obesity

Prevalence: Up to 40% of patients are obese (> 20% above ideal body weight) within 1 year of transplantation. Weight tends to increase for at least 2 years following transplantation, and weight gains of 20%-30% above preoperative weight are not uncommon.

Clinical Management:

- General: As in the general population, management of weight gain is to reduce caloric intake and to increase exercise.

Renal Insufficiency

Epidemiology: Prior to liver transplantation, renal insufficiency may go unrecognized in many cirrhotic patients. Poor muscle mass and impaired hepatic synthesis of creatinine may lead to an underestimation of glomerular filtration rate based on serum creatinine levels. Several liver diseases, including chronic viral hepatitis, autoimmune hepatitis, and primary biliary cirrhosis, are associated with glomerulonephritis. Early onset of chronic renal failure in patients transplanted for chronic hepatitis C infection may be due to cryoglobulinemia-associated glomerulonephritis.

Key facts are

- The majority of recipients demonstrate decreased renal function within months of liver transplantation.
- Serum creatinine concentrations > 1.6 mg/dl (140 mmol/l) are found in more than 75% of liver transplant recipients after 3 years of follow-up.
- The progression to end-stage renal failure is predicted by significant renal impairment as early as 1 year after liver transplantation.

- Between 4% and 10% of liver allograft recipients develop end-stage kidney failure by 10 years. Postliver transplant diabetes mellitus, hypertension, and viral hepatitis may all increase the risk of progression to end-stage renal disease. Mortality has been shown to be higher in postliver transplant patients whose renal failure progresses to the point of requiring dialysis.

Z-SCORES

Number of standard deviations from mean, a marker of mineral bone density

Pathogenesis: Postliver transplant renal insufficiency is a direct consequence of calcineurin inhibition. Acute elevation of serum creatinine is frequently the result of calcineurin inhibitor toxicity and responds to dose reduction. Chronic elevations in serum creatinine rarely return to normal levels after reduction of calcineurin inhibitor doses. Kidney biopsy in liver transplant recipients with sustained reduction in GFR shows interstitial fibrosis and patchy glomerular loss and hypertrophy of unaffected glomeruli.

Clinical Management: The goals of therapy are to

- Minimize the use of calcineurin inhibitors. If renal failure persists despite reducing calcineurin inhibition, consider switching to alternative immunosuppressive therapy.
- Avoid other nephrotoxic drugs.
- Control hypertension.
- Control diabetes mellitus.

Renal transplantation is appropriate in established renal failure arising after liver transplantation.

Osteoporosis and Osteopenia

DEXA SCAN

Dual energy x-ray absorption

Prevalence: Chronic liver disease is associated with osteopenia due to low bone turnover.

Risk factors:

- Chronic cholestasis
- Female gender
- Older age
- Cessation of menses
- Cigarette smoking
- Poor dietary calcium intake
- Alcoholism
- Calcineurin inhibitors
- Maternal history of fracture

Key facts are

- Bone turnover is greatly increased after transplantation due to excessive osteoclastic activity. Cyclosporin and tacrolimus increase osteoclastic activity and bone turnover. Corticosteroids reduce new bone formation.
- Bone loss increases rapidly over the first 3 months following liver transplantation. Z-scores (number of standard deviations from the normal mean), a marker of bone mineral density, commonly reach –2 standard deviations—the range for osteoporosis. Each standard deviation decrease in bone mineral density is associated with a 1.5- to 2.8-fold increase in the risk of hip fracture in postmenopausal women.
- Atraumatic vertebral fractures have been reported in up to 30% of liver transplant recipients within the first 6 months of transplant. Bone density tends to improve over the first postliver transplant year, approaching pretransplant levels but remains below that of the general population.

Clinical Management: Spontaneous fractures are a late sign of bone loss; therefore, management focuses on screening and prevention.

Patients should be screened pretransplant for osteopenia by (dual energy x-ray absorption) DEXA scan or early posttransplant

Medication:

- Those with osteopenia z-scores between –1 and –2 should be treated with calcium (1 g per day) and vitamin D (400 IU/day) supplementation.
- Those with z-scores less that –2 should receive bisphosphonates in addition to the calcium and vitamin D supplementation.

Other measures:

- Weight-bearing exercise (e.g., walking) and strength training in conjunction with calcium

and vitamin D supplementation decrease the rate of bone loss in postmenopausal women.

It is advisable to recheck bone mineral density 1 year after transplantation. In patients with z-scores greater than –1, repeat DEXA can be deferred for about 5 years.

Malignancy

The risk of malignancy is increased in liver transplant recipients.

Skin Cancer

Prevalence: Skin cancer is the most common cancer after liver transplantation. It tends to behave more aggressively than in the nontransplant patient. More than 5% of cases are metastatic. This compares to < 1% for the general population. The relative risks of individual immunosuppressive medicines either alone or in combination remain unknown.

The prevalence of Kaposi's sarcoma is also increased in solid-organ transplant recipients although less strikingly than in the HIV-positive population. Human herpes virus-8 (HHV-8) has been implicated in Kaposi's sarcoma in both immunosuppressed and immunocompetent individuals.

HPV

Human papillomavirus

The increase in nonmelanomatous skin cancer seen in liver transplant recipients seems to be largely due to increased prevalence and activity of human papillomavirus (HPV) in the immunesuppressed host.

Clinical Management:

- Education is key. All transplant recipients should be informed of their increased risk of skin cancer.
- Avoidance of sun: They should be educated in sun-protective practices, including minimizing sun exposure between 10:00 and 16:00, the use of protective clothing and broad brimmed hats, and the use of sunscreen and lip-balm with a sun protection factor of 15 or higher.
- Self-examination: Patients should be encouraged to examine their skin. They should also have a formal skin inspection at least annually, and should any suspicious lesions be seen, these should be referred to a dermatologist for further evaluation.

Oral Cancer

- Oral cancer is associated with smokeless tobacco, alcohol consumption, and sun exposure.
- Both EBV and HPV are associated with hairy leukoplakia, which can be seen as feathery appearing plaques on the tongue or buccal mucosa. Macroscopically they are indistinguishable from premalignant leukoplakia and should be biopsied.
- Erythroplakia—a red hyperplastic area of mucosa—is a premalignant condition.

Carcinoma of the Uterine Cervix

Prevalence: The prevalence of cervical intraepithelial neoplasia in transplant recipients is approximately 5-fold that of immunocompetent controls. Seventy-five percent to 93% of cervical cancers or carcinomas in situ are associated with HPV.

Clinical Management: All female liver transplant recipients over the age of 18 years who are sexually active should undergo annual cervical smear cytology tests. Patients with cervical dysplasia or carcinoma in situ should be referred to a gynecologist. The role of reduced immunosuppression as part of a treatment plan for cervical carcinoma in situ or cervical carcinoma is uncertain.

Other Cancers

Liver and other transplant recipients are at increased risk of cancer of the vulva and perineum, anal cancer, hepatobiliary tumors, and colon cancer. Routine screening is important, and physicians should maintain a high index of suspicion for cancer development in liver transplant recipients.

Infections after Recovery from Liver Transplantation

Infection accounts for 15%-20% of deaths in long-term liver transplant survivors.

- Viral infections: Viral infection with CMV, EBV, HPV-6, VZV, and parvovirus B19 tend to occur within 3 months of transplant but may occur later. Patients seronegative for vari-

Table 3 | **Live and Attenuated Vaccines**

Varicella
BCG
Yellow fever
Typhoid (for travelers)
Oral polio
MMR: although an attenuated live vaccine has been deemed safe and is recommended in those liver transplant recipients who were not vaccinated prior to liver transplant

cella zoster, who are exposed to varicella, should receive immunoglobulin. The development of primary varicella zoster infection should be considered a medical emergency in the posttransplant patient, and intravenous acyclovir (10 mg/kd) should be started immediately.

Tuberculosis

Tuberculosis occurs in < 1% of patients at any time after liver transplantation. The risk of disseminated tubercular disease (25%) and of death (20%) is much greater among solid organ recipients than for the general population.

Diagnosis is made by a combination of staining for acid-fast bacilli, culture of the organism, histopathology, and tuberculin skin testing.

Treatment with standard therapy is problematic.

- Isoniazid: There is a high rate of hepatic dysfunction (33%) particularly with isoniazid use.
- Rifampicin induces cytochrome P450 3A, and thereby greatly accelerates metabolism of cyclosporin and tacrolimus. Despite careful monitoring of levels, rejection is a common occurrence (30%-50%) in liver transplant recipients receiving rifampicin in conjunction with cyclosporin. Conversely, there is a risk of cyclosporin or tacrolimus toxicity when the dose of rifampicin is reduced or withdrawn.
- Other drugs: Due to the high toxicity with conventional therapy, an alternative approach using ethambutol and ofloxacin as maintenance therapy has been suggested. Although promising, this regimen has not yet been widely tested.

Vaccinations

Immunosuppressed patients should not be given live or attenuated vaccines (Table 3).

Common Causes of Morbidity in Liver Transplant Recipients

Insomnia

Early postoperative insomnia is related to corticosteroids and/or calcineurin inhibitor. Patients frequently feel hyperalert and have difficulty achieving a sufficiently relaxed state in which to sleep. Postoperative pain, especially right posterior rib pain (which can last several months), and adjustment to the transplant compound the problem. Most patients respond to reassurance and analgesia. Relaxation exercises and good sleep practices may also help.

Lassitude

Tiredness is a common complaint after liver transplantation and may have many contributing factors including medications. Recurrence of chronic hepatitis C is often associated with lassitude. Lassitude may be a manifestation of depression.

Cosmetic Concerns

Hirsutism: May be due to cyclosporin and exacerbated by nifedepine or corticosteroids. Treatment is switching to tacrolimus.

Gum hypertrophy: May be caused by poor dental hygiene and cyclosporin and is exacerbated by nifedepine.

Acne: Corticosteroids can cause acne. Fortunately this tends to improve with dose reduction and with time.

Cutaneous warts: Are more common in transplant recipients, affecting 25%-90% of recipients. They tend to be quite exuberant and difficult to treat. Flat warts may become the site of future squamous cell carcinoma.

Musculoskeletal Pain

Back pain particularly over the right posterior ribs can persist for many months postliver transplant. Its persistence and severity surprises many patients, and reassurance is in order. Simple analgesia can be used. Other more focal, severe, or persistent musculoskeletal pains should raise the suspicion for osteoporosis with secondary fracture, especially of the vertebrae, osteonecrosis particularly of the hip joints, and osteomyelitis or abscess.

Seizures

New seizures occur most commonly within the first postoperative week and are related to intraoperative metabolic changes, calcineurin inhibitor toxicity, central pontine myelinolysis, intracranial bleed, or infection. Seizures occurring in the later weeks following liver transplant are less likely to be due to electrolyte disturbance or central pontine myelinolysis, and drug toxicity and infection are more of a concern.

Investigations: Neurological examination for focal deficits; biochemical testing for electrolyte disturbances, including hypomagnesemia and cyclosporin or tacrolimus levels; blood count and coagulation profile to check for coagulopathy or infection; computed tomography (CT) or magnetic resonance imaging (MRI) of the head for space-occupying lesions; and an examination of the CSF to rule out bacterial or opportunistic infection in the immunocompromised host. Both cyclosporin and tacrolimus can cause diffuse white matter changes, which are seen on MRI more readily than on CT.

Management focuses on correction of underlying metabolic or infectious problems and the use of anticonvulsant agents. Consideration must be given to the risk of interactions between immunosuppressive agents and anticonvulsants.

Headache

Headache and tremor are common complaints. Milder headaches, often associated with tremulousness, are usually due to calcineurin inhibitor toxicity. An exacerbation of previously existing migraine headaches may also occur due to cyclosporin or tacrolimus.

Evaluation consists of examination to rule out focal neurological deficits, screening for cyclosporin or tacrolimus toxicity or metabolic disturbances, and CT or MRI to rule out space occupying lesions.

Treatment: Simple analgesia and where possible reduction in the calcineurin inhibitor doses. Where headaches are severe, narcotic analgesia may be required. Antidepressants, calcium channel blockers, and β-blockers have also been used with varying success. Migraine may respond to sumatriptan, although systemic hypertension may limit its use.

Fine Tremor

Fine tremor is common in the liver transplant recipient. It is related to calcineurin inhibitor use and may respond to lowering of the dose.

Psychiatric disturbances such as short-term anxiety, depression, or adjustment disorders are common after liver transplant. Less commonly they represent an atypical presentation of an organic syndrome, for example, drug toxicity or infection. Liver transplant recipients with a history of addiction should be monitored for evidence of relapse. Prompt referral to substance abuse services may be helpful.

Pregnancy and Reproductive Health

Menstrual Function

Recovery of menstrual function in premenopausal females and of andrological function in males occurs after liver transplantation. Menses typically resume within a few months of transplantation.

Preconception Management

Most centers advise waiting 1 to 2 years after liver transplantation before becoming pregnant. Barrier or oral contraception should be considered during this period. The 1- to 2-year delay allows for the patients to fully recover from the transplant, for opportunistic infection prophylaxis to be discontinued, and for immunosuppression to be reduced.

Table 4 | **Routine Health Screening of Liver Transplant Recipients**

Disease	Orthotropic Liver Transplantation pat	US Population
Hypertension	Every visit	Every 2 years if previously normotensive
Renal insufficiency	Serum creatinine every visit	No recommendations
Hypercholesterolemia	At 6 months, 1 year, 2 years, and if normal every 3-5 years thereafter	Every 5 years in men aged 35-65 years and in women aged 45-65 years
Diabetes mellitus	Gluc > 160 on "routine labs" are grounds for a formal oral glucose tolerance test	Screening in the asymptomatic general population is not recommended
Cigarettes	Counseling on smoking cessation	Counseling on smoking cessation
Osteoporosis	DEXA pre-OLT (or post-OLT)	DEXA in early postmenopausal women
Breast Cancer	Self-breast exam monthly Annual clinical breast exam age 40-69, possibly longer Mammography 50-69	Self-breast exam monthly. Annual clinical breast exam age 40-69, possibly longer. Mammography 50-69
Cervical cancer	Papanicolaou smear every year. Decrease to every 3 years if several normal tests	Papanicolaou smear every 3 years (assuming prior smears were normal) until age 65
Colon cancer	As for general population annual colonoscopy for those with history of IBD	Flexible sigmoidoscopy ever 3-5 years age 50-70 years old, begin earlier in those at higher risk
Prostate cancer	Annual digital rectal exam ± prostatic-specific antigen after age 50	Annual digital rectal exam ± prostatic-specific antigen after age 50
Skin cancer	Monthly self-exam. Annual physician-provided skin exam	Not recommended
Dental care	Routine oral hygiene (brushing and flossing of teeth) 6 monthly visits to dentist	Routine oral hygiene (brushing and flossing of teeth)
Oral cancer	Annual exam by dentist	Not recommended

Conception should be planned when graft function is stable and good. Some immunosuppressant drugs are teratogenic. The immunosuppressive regime may be modified to avoid these drugs. Due to the increased prevalence of both maternal and fetal complications, these are "high-risk" pregnancies and should be closely monitored by both the transplant and obstetrical teams.

Pregnancy

Data from the National Transplant Pregnancy Registry (NTPR) record 2017 pregnancies in 732 women or fathered by 603 men who were recipients of solid organ transplants. (See Armenti VT, Wilson GA, Radomski JS, Moritz MJ, McGrory CH, Coscia LA. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 1999;13:111-119.) No pattern of congenital anomaly has been noted. Of the 175 offspring studied, all of whom are children of female kidney transplant recipients, 76% were live born, 14% suffered spontaneous abortion, and 10% were stillborn, ectopic pregnancies, or electively aborted. There was no significant developmental delay in 84% of the children, but 3 children (1.7%) had major disabilities. In 72 female liver transplant recipients, 119 pregnancies were associated with 91 (76%) live births. This compares with the general population wherein 10% of pregnancies are lost before 20 weeks, with late fetal loss of approximately 0.5%. It is likely that there is underreporting of early pregnancy loss in the NTPR. Thirty-seven percent of live born children were premature (< 37 weeks gestation), and 32% were low birth weight (< 2500 g).

Regarding the health of the expectant mother, the risk of acute cellular rejection in the pregnant liver transplant recipient seems to be increased, either occurring during pregnancy or within 3 months of delivery. Acute cellular rejection was associated with poorer fetal outcome and increased risk of recurrent rejection. Thirty-three percent of pregnant liver transplant recipients will develop hypertension and 10%-15% diabetes mellitus. Hypertension, diabetes, and infections should be meticulously managed. Consideration should be given to stress dose steroids for mothers requiring cesarean section.

Breast Feeding

Most immunosuppressive drugs are secreted in breast milk. Consequently, breast-feeding should be avoided.

Lifestyle

Liver allograft recipients should be encouraged to return to a normal healthy lifestyle, with appropriate health maintenance (see Table 4).

Selected Reading

1. Abbasouglu O, Levy MF, Brkic B, Testa G, Jeyarahaj DR, Goldstein RM, et al. Ten years of liver transplantation. **Transplantation 1997;64(12):1801-7**.
2. Midtvedt K, Neumayer HH. Management strategies for posttransplant hypertension. **Transplantation 2000;70(11):SS64-9**.
3. Feller RB, McDonald JA, Sherbon KJ, McCaughan GW. Evidence of continuing bone recovery at a mean of 7 years after liver transplantation. **Liver Transplant Surg 1999;5(5):407-13**.
4. Otley CC, Pittelkow MR. Skin cancer in liver transplant recipients. **Liver Transplant 2000;6(3):253-62**.
5. Meyers BR, Papanicolaou GA, Sheiner P, Emre S, Miller C. Tuberculosis in orthotopic liver transplant patients: increased toxicity of recommended agents; cure of disseminated infection with nonconventional regimens. **Transplantation 2000;69(1):64-9**.
6. Armenti VT, Wilson GA, Radomski JS, Moritz MJ, McGrory CH, Coscia LA. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. **Clin Transpl 1999;13:11-119.**