Pregnancy in the Liver Transplant Recipient

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During gestation, the woman’s body undergoes various changes, and the line between physiology and pathology is very thin even in healthy women. Today, many of the liver transplant recipients are young women, who at one point in their lives may consider the possibility of pregnancy. Clinicians have to counsel them about the time of conception, the risk of miscarriage, the deterioration of the mother’s health status, and the risk of birth defects. This review, based on our 20 years of clinical experience and up-to-date literature, provides comprehensive guidelines on pregnancy management in liver transplant recipients. Pregnancy in liver transplant recipients is possible but never physiological. Proper management and pharmacotherapy lowers the incidence of complications and birth defects. Critical factors for perinatal success include stable graft function before pregnancy, proper preparation for pregnancy, and cautious observation during its course.

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It is estimated that 8% of liver transplantation (LT) recipients are women of reproductive age, and another 5% are girls, most of whom will live until reproductive age and will consider the possibility of pregnancy.1,2 The number of patients who are undergoing solid organ transplants is increasing as well as their quality of life (QOL) and chance for pregnancy. Pregnancy and delivery in patients after LT is feasible but burdened with an increased risk of premature birth, intrauterine growth restriction, graft dysfunction, and cesarean section.3-5 Recent studies suggest that the liver plays an important role in fertility not only by sustaining body metabolic and hormonal balance but also by producing fetuin-B. This protein sustains fertility by inhibiting ovastacin, a protease known to trigger hardening zona pellucida of the oocyte. Without fetuin-B permeability of zona pellucida would be locked before gamete fusion could even happen.6

There are still questions without clear answers concerning safety of breastfeeding and adjusting the dose of immunosuppressants in the perinatal period. Even before LT became standard procedure in end-stage liver failure, negative effects of azathioprine (AZA) on neonates had been excluded. Although it is known that the exposure to immunosuppressants via breast milk is less than during the pregnancy, in many countries, mothers are advised to bottle-feed. There is evidence that maternal T cells actively respond to fetal antigens and can recognize and kill fetal cells in maternal blood.7 However, the mechanisms and dynamics of allograft tolerance during pregnancy are still unknown.8
Despite numerous reports, doubts still exist regarding the optimal method of managing female patients of reproductive age. Concerns relate to choosing the time of conception, the risk of miscarriage, the deterioration of the mother’s health status, and the risk of birth defects in children. The following review, based on our own 20-year experience and the relevant literature, is a comprehensive guideline on pregnancy management, from obstetric care to hepatological viewpoints. Ethics committee approval was not obtained for this article. The manuscript is an analysis of our prior clinical experience in treating pregnant women after LT confronted in conjunction with the current literature. All patients described had signed informed consent for use of their medical history for scientific purpose at the moment of hospital admission.

Before Conception

CONTRACEPTION COUNSELING

In high-risk patients with chronic concomitant diseases, pregnancy should be carefully planned. Only 29% of patients after LT were given an effective contraception. A developing fetus in an LT patient is exposed to the underlying disease and iatrogenic effects of immunosuppressive drugs. Our observations show that up to 50% of pregnancies in this group (aged 18-45 years) are unplanned. These data could be accidental and could be a result from low education level of patients because in reports on small but closely followed up groups given oral contraceptives, no pregnancies were noticed at up to 12 months of observation. Women with poor liver function suffer menstrual disorders, with amenorrhea observed in up to 50% of patients. Dysfunction of the hypothalamic-pituitary-ovary axis is observed, which leads to a reduction in the release of gonadotropins and circulating levels of sex hormones. Hence, pregnancy during decompensated cirrhosis is rare. Successful LT restores normal hormonal cycle within a few months. Our studies show that 74% of women recover regular menstrual cycles within a year after LT. It is estimated that 80%-90% of women at reproductive age after LT have a chance to become pregnant. There are reports on the safe use of highly effective contraceptive methods (transdermal, oral contraception, and intrauterine device) in this group of patients, and therefore, we recommend cautious use of the method best suitable for a patient’s lifestyle and the regular control of liver function.

FERTILITY PRESERVATION AND ASSISTED REPRODUCTION TECHNIQUES IN TRANSPLANT PATIENTS

There are various indications for LT such as occasional poisoning or intoxication, hepatotropic viruses infection, genetic disorders, and cancer. Some patients, despite a young age and a full recovery of liver function, will be castrated by the administration of chemotherapy or aggressive radiation treatment. Some couples need fertility treatment for reasons other than liver problems. For young women, the preservation of reproductive potential is important for QoL. Concerns regarding infertility may affect treatment decisions even in very serious diseases. Currently, few researchers have addressed the problem of infertility in posttransplant patients. Clinicians should recognize the possibility of an in vitro treatment that may result in a successful pregnancy, even when both partners have undergone transplantation procedures. In the case of patients who are expected to receive gametotoxic treatment, it is advisable to present current fertility preservation techniques such as transposition of the ovaries away from the area targeted for radiation, ovarian suppression using gonadotropin (GnRH) analogues such as goserelin and leuprorelin acetate, or cryopreservation of oocytes or ovarian tissue.

CHOOSING THE TIME FOR PREGNANCY

The immunosuppressive therapy may be a contraindication for pregnancy. It is known that all currently used immunosuppressive drugs pass through the placental barrier and may cause a variety of intrauterine disorders. Teratogenic effects of immunosuppressive therapy were summarized in Table 1.

By far, the highest rate of fetal complications was observed after mycophenolate mofetil (MMF) treatment, which alters the function of B and T lymphocytes. The most common defects associated with its use are the lack of an ear canal, microtia, cleft palate, and early pregnancy loss. Hence, the need to modify the immunosuppressive regimen prior to a planned pregnancy is crucial and is recommended for at least 6 weeks prior to fertilization. MMF is a confirmed teratogen associated with an increased rate of spontaneous abortion and congenital malformation compared with other immunosuppressants, and therefore, it must not be used during pregnancy. It should not be prescribed.
to women of childbearing potential unless they are using highly effective contraception.\(^{(45,46)}\)

Tacrolimus (Tac) appears to be effective in the maintenance of adequate immunosuppression during pregnancy.\(^{(43)}\) Women with poor or unstable liver function are particularly susceptible to rejection if they become pregnant.\(^{(11)}\) Pregnancy can be advised in women who are maintained on low-dose immunosuppressive therapy with proper allograft function, which is defined as stable levels of bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Even though we have encountered patients with physiological pregnancy that was conceived 1 month after LT, it is usually achieved between 1 and 2 years after transplantation.\(^{(47)}\) Stable immune modulation, a washout period of drugs inappropriate for fetal development, and completed postoperative healing are imperative for counseling toward pregnancy.

PREPARING FOR PREGNANCY

For LT patients with a stable graft function and without failure of other organs, a single visit to the hepatologist may be sufficient in order to consult immunosuppressive therapy. In patients with normal function of the transplanted organ, odds of spontaneous abortion are 25% (19% for spontaneous and 6% for therapeutic).\(^{(47)}\)

A pap smear should be taken approximately 3 months before pregnancy, and eventual vulvovaginitis needs to be treated. The patient has to be counseled about the changes that will occur in her body and life. The pharmacotherapy of comorbidities, diet, job, or risk associated with planned trips and diagnostic tests should also be considered (x-ray and computed tomography performed in the first phase of the menstrual cycle). It is important to remember to change the group of antihypertensive drugs from diuretics and angiotensin-converting enzyme (ACE) inhibitors to alpha-methyldopa before pregnancy or at its very beginning. In many countries, the switch from oral hypoglycemic agents to insulin is recommended. A preconception “to do list” is summarized in Table 2.

### After Conception

MANAGEMENT OF PREGNANCY

In healthy women, obstetrical checkups should follow the standard intervals proposed by the Fetal Medicine Foundation, but because of immunological changes induced on the fetal-maternal interface LT patients need closer attention.

Although physicians should look for signs of liver failure, these may be difficult to identify because symptoms such as increased sleepiness, increasing waist circumference, or eating disorders can also be caused by pregnancy.

Liver Graft Rejection and Graft Failure

Normal hepatocytes have only weak expression of human leukocyte antigen (HLA) class I and class II, and liver rejection often occurs as an acute process mediated by B cells.\(^{(48)}\) During pregnancy, the placental fraction of interleukin (IL) 10 secretion can trigger higher activation of B cells, resulting in rejection episodes. Moreover, we have to remember that the immunological recipient-graft balance can be disturbed by adding a third party: fetal microchimeric cells, which

<table>
<thead>
<tr>
<th>FDA Class(^{{(34)}})</th>
<th>Teratogenic Effect in Animal Studies</th>
<th>Nephrotoxicity</th>
<th>Effect on Blood Pressure</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>B</td>
<td>none</td>
<td>+/−</td>
<td>↑↑↑†</td>
</tr>
<tr>
<td>CsA</td>
<td>C</td>
<td>+</td>
<td>++</td>
<td>↑↑↑†</td>
</tr>
<tr>
<td>Tac</td>
<td>C</td>
<td>none</td>
<td>++</td>
<td>↓</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>C</td>
<td>none</td>
<td>+</td>
<td>↓</td>
</tr>
<tr>
<td>AZA</td>
<td>D</td>
<td>+‡</td>
<td>+/−</td>
<td>+/−</td>
</tr>
<tr>
<td>MMF</td>
<td>D</td>
<td>+</td>
<td>+/−</td>
<td>+/−</td>
</tr>
</tbody>
</table>

NOTE: No large controlled studies on the effect of immunosuppressive drugs on the course of pregnancy and fetal development have been reported.\(^{(3)}\)

*Impact on the development of the fetus is low because only 10% of the dose enters the fetal circulation.\(^{(29)}\)

†CsA accelerates the metabolism of nifedipine, reducing its effectiveness in the treatment of hypertension which may be a side effect of CsA.\(^{(27)}\)

‡Data are from animal studies. In humans, despite the passage through the placenta, the fetus does not have pyrophosphorylase inosinate which converts 6-mercaptopurine in the final metabolite known as thiouric acid,\(^{(31)}\) thus it is successfully applied in pregnant women.
Examination—do not forget to check for the following:

- Onset of symptoms.
- But they should be implemented immediately after the standard regimens of antibiotic therapy can be used, in infections, patients do not require hospitalization and reduction of the immune system activity. For most genic fetus developing in the uterus corresponds to the suppression. The physiological response to a semiallogenic transplant model which, despite the dis-similarity in a mother’s HLA, is not rejected.\(^{(49-51)}\) In the serum of pregnant women, the presence of fetal cells persisting up to 27 years after delivery were discovered.\(^{(58)}\) The mechanisms of the protection of the fetus against the mother’s immune system results from the cross-talk among pregnancy-related hormones and proteins and maternal immune cells, like decidual macrophages which are responsible for creating a homeostatic environment at the fetal-maternal interface.\(^{(54,55)}\) Together with regulatory T cells (Tregs) and a small population of dendritic cells, they come into contact with invading extravillous trophoblast cells and adapt the mother’s immune system to the fetal antigens.

Can pregnancy induce the change in immunology of the organ recipient and contribute to improved graft survival? This hypothesis is supported by the studies confirming that the interaction between mother and fetus is not limited to the uterus. For example, Cham-ley et al.\(^{(56)}\) isolated trophoblast cells from the serum of pregnant women. They found that trophoblast cells that underwent physiological apoptosis increase the tolerance of macrophages, and necrotic abnormal fragments of trophoblasts promoted an enhanced immune response. Furthermore, necrotic cells in the endothelium increase expression of intercellular cell adhesions molecule 1, monocyte adhesion and production of proinflammatory IL6, lipopolysaccharide, and phorbol 12-myristate 13-acetate.\(^{(57)}\)

In the serum of pregnant women, the presence of fetal cells persisting up to 27 years after delivery were discovered.\(^{(58)}\) Gestation is associated with an increased...

### TABLE 2. Preconception Counseling: Points to Remember

<table>
<thead>
<tr>
<th>Criteria of (relatively) safe pregnancy</th>
<th>Patient and her partner must be counseled about the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good general health, 1 year after LT</td>
<td>Risk associated with pregnancy for her health and life</td>
</tr>
<tr>
<td>Normal USG liver image</td>
<td>Risk of fetal growth restriction and preterm birth</td>
</tr>
<tr>
<td>No acute rejection (biopsy not recommended)</td>
<td>Risk of health status deterioration after pregnancy</td>
</tr>
<tr>
<td>No hypertension (eventually controlled with 1 drug)</td>
<td>The need for folate acid supplementation for 2-3 months before pregnancy</td>
</tr>
<tr>
<td>Stable liver function</td>
<td>Risk of complications of pregnancy</td>
</tr>
<tr>
<td>Immunosuppression: P &lt; 15 mg/day; AZA &lt; 2 mg/kg/day; CsA or therapeutic doses of Tac</td>
<td>The need to ensure care for the child, including the ability to provide highly specialized childcare in the event of premature delivery</td>
</tr>
<tr>
<td>Normal: transaminases, platelets, plasma protein, albumin, and LDH</td>
<td>The basic laboratory tests and necessary vaccinations for all pregnant women</td>
</tr>
</tbody>
</table>

The basic laboratory tests and necessary vaccinations for all pregnant women:

- **Previous History**
  - Genetic and congenital defects in past pregnancy: genetic counseling for both parents
  - Early pregnancy loss: vaginal progesterone 2 \(\times\) 200 mg/day until 16 weeks
  - Diabetes: glycemia monitoring 4-9/day (if fasting > 5.1 mmol/L or + postprandial > 7.2 mmol/L, introduction of insulin, preferably in pump)
  - Hypertension: exclude ACE inhibitors, if possible switch to monotherapy with \(\alpha\)-methyldopa, eventually add labetalol.
  - Previous pregnancies and childbirth: screen for preterm birth and eclampsia

- **Examination**—do not forget to check for the following:
  - Skin: look for vascular lesions, jaundice, and edema
  - Stool and urine color: look for signs of liver dysfunction
  - Ask about itching, bruising, nosebleeds
  - Blood pressure: check on every visit + daily self-monitoring by the patient. If > 150/100 mm Hg, refer to Fetal Medicine Unit.
  - Weight gain/weekly plus abdomen circumference: for edema and ascites
  - Every 4 weeks, 24-hour urine collection: if protein > 500 mg/24 hours, repeat the test immediately, if > 1000 mg/24 hours, refer to Fetal Medicine Unit for further blood work (transaminases, LDH, D-dimer, platelet count).
  - During obstetric USG, look for maternal ascites.

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  - During obstetric USG, look for maternal ascites.
secretion of IL10, which activates B cells that are responsible for the memory of the immune system. It may suggest a long-term effect of selective immunosuppression and forecast better transplant survival in women who underwent an uncomplicated pregnancy. However, confirmation of this suggestion requires further detailed observations.

**MANAGEMENT OF PREGNANCY: BIOCHEMICAL TESTS AND MICROELEMENT SUPPLEMENTATION**

For pregnant women after LT, all standard tests mandatory during pregnancy should be done (Table 3).

Thrombocytopenia is a challenge in many post-LT patients. In the pregnant population, a decrease in the level of platelets requires hospitalization in order to perform a thorough evaluation of liver function. Thrombocytopenia is not only a contraindication to epidural analgesia due to the increased risk of bleeding into the cerebrospinal fluid, but also one of the main symptoms of grievous perinatal complications such as hemolysis, elevated liver enzymes, low platelets syndrome, and eclampsia. Mild thrombocytopenia can occur during the second and third trimesters due to physiological hemodilution, but each sudden decrease or result below $100 \times 10^3$ mm$^3$ needs accurate investigation.$^{(59-61)}$ Accompanying coagulation disorders may cause increased blood loss during delivery or cesarean section. In order to counteract this risk, transfusion of platelets or blood cell concentrate and plasma clotting factors (cryoprecipitate) may be performed. Stabilization of the level of platelets allows for the safe management of delivery in the spinal anesthesia avoiding cesarean section under general anesthesia. Analysis of the concentration of immunosuppressive drugs should be prescribed by a transplant physician in order to correct the dose every 4–8 weeks. An increase of serum volume in pregnancy can lead to a decrease of drug concentrations. On the contrary, excess storage in the third space and adipose tissue is also possible. Therefore, we recommend that immunosuppressant concentrations are assessed every 4 weeks and that the doses are adjusted accordingly.

Many physicians continue AZA throughout pregnancy, but regimens with MMF and AZA should be avoided if possible because of the increased risk of auditory nerve agenesis in children. In the treatment of relatively small groups of pregnant post-LT patients, we have to learn from other specialties. Recently published systematic literature reviews by the European League Against Rheumatism show compatibility with pregnancy and lactation for AZA, cyclosporine A (CsA), Tac, and glucocorticosteroids.$^{(25)}$ Considering the pros and cons, we suggest the introduction of schemas based on CsA, Tac, and steroids in female patients preparing for pregnancy.$^{(12)}$

Recommendations for iron, vitamin D, iodine, and trace element supplementation in patients after LT do not deviate from the standard population (Table 4).$^{(26–30)}$

**MEDICAL IMAGING AND BIOPHYSICAL PROFILE DURING PREGNANCY**

Antenatal screening should include 3 ultrasound scans. LT alone is not an indication for more frequent obstetric or liver ultrasound. In LT patients, fetal hypotrophy and cholestasis of pregnancy are often observed.$^{(5,11,13)}$ Fetal biometry at 30-34 weeks could identify a high proportion of pregnancies that will deliver small for gestational

### TABLE 3. Routine Blood Work in Pregnancy

<table>
<thead>
<tr>
<th>Viral Status (First and Third Trimester)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>IgG serum antibodies (First, second, and third trimester, in Rh(-) patients injection of 1500 U of immunoglobulin in 28 weeks)</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Morphology, urinalysis, 24-hour urine collection for detecting proteinuria, ALT and AST, total bilirubin, creatinine, LDH, and glucose</td>
</tr>
<tr>
<td>Rubella</td>
<td>concentration should be checked every 4 weeks</td>
</tr>
<tr>
<td>Syphilis</td>
<td></td>
</tr>
<tr>
<td>Varicella-zoster</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td>Herpes</td>
<td></td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Patients on CsA are at high risk of thrombocytopenia. If platelet count is $<150 \times 10^3$/mL, then control weekly. If $<50 \times 10^3$/mL, then consider platelet transfusion 24 hours before delivery. In case of rubella and varicella, vaccination 12 weeks prior pregnancy is optimal. Viral status is usually known in LT patients. Testing should be adjusted to national guidelines.
age neonates. In such cases, middle cerebral and umbilical artery Doppler (cerebroplacental ratio) can help to assess the risk of intrauterine death.

Pregnancy in chronic liver disease patients in our opinion needs weekly observation of fetal distress symptoms during the late third trimester. In an uncomplicated pregnancy and eutrophic fetus development, weekly cardiotocography and amniotic fluid observation starting from the 36th week should be implemented. The recommended biophysical tests are summarized in Table 5.

**WHEN SHOULD HOSPITALIZATION BE ADVISED?**

The fact that a pregnant woman underwent LT in the past does not itself constitute an indication for hospitalization. Recommendations for physical activity, work, travel, and sex life in uncomplicated pregnancy in this group of patients should not differ from recommendations for the general population. Concomitant diseases can complicate the course of every pregnancy, especially in more mature patients. The most frequent comorbidities in pregnancy together with diagnostic criteria and treatment suggestions are listed in Table 6.

**Delivery and Postpartum Care**

**WHEN AND HOW TO COMPLETE PREGNANCY**

Patients pregnant after LT are at risk of a preterm birth. Therefore, they may benefit from the standard intramuscular doses of steroids to accelerate fetal lung development between 24 and 34 weeks. However, in asymptomatic patients with normal laboratory test results and with eutrophic fetus development, it should not be a routine procedure. Isolated fetal hypotrophy is not an indication for early completion of the pregnancy. Our clinical experience suggests that current criteria (American College of Obstetricians and Gynecologists and International Society for the Study of Hypertension in Pregnancy) seem not suitable for patients with chronic internal diseases,

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**TABLE 4. Diet and Microelement Supplementation in Pregnancy**

<table>
<thead>
<tr>
<th>Diet</th>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance of allergenic, heavy foods, as well as foods that cause constipation</td>
<td>40%-50% carbohydrates (mainly complex: vegetables, bread, cereals); 20%-30% protein; 20%-30% fat</td>
<td>If possible, maintain a regular, moderate physical exertion</td>
<td>Increase in calorie intake by 360 kcal/day →</td>
<td>Intake of 30-35 kcal/kg of ideal body weight →</td>
</tr>
<tr>
<td></td>
<td>Intake of 30-35 kcal/kg of ideal body weight, obese patients: 12-24 kcal/kg oral glucose tolerance test should be done.</td>
<td>Increase in calorie intake by 475 kcal/day →</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 5. Recommended Plan of Biophysical Tests During Pregnancy in Organ Recipients**

<table>
<thead>
<tr>
<th>Test</th>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>11 + 3 to 13 + 6 weeks: scan for aneuploidy and major genetic disorders</td>
<td>20-24 weeks: anomaly scan according to Fetal Medicine Foundation guidelines, amniotic fluid amount</td>
<td>32 weeks: well-being scan plus measurement of the amount of amniotic fluid, plus assessment of blood flow to the placenta and fetus by color Doppler ultrasound (UA, MCA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypotrophy, oligohydramnios, GDM: 2/week from 34 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotrophy plus oligohydramnios: 2/week</td>
<td>Eutrophic 36 weeks: 1/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If there is a decrease in fetal movement, perform immediately</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 hour after breakfast, lunch, and dinner, in quiet environment, up to 10 movements. If 6-9 movements, 15-minute walk plus a high glucose snack and counting for 1 more hour.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If there are &lt; 6 movements, then do a cardiotocogram.</td>
</tr>
<tr>
<td>Cardiotocogram</td>
<td>None</td>
<td>Fetal hypotrophy: 1/week</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotrophy plus oligohydramnios: 2/week</td>
<td></td>
</tr>
<tr>
<td>Fetal movement count</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

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**TABLE 6. Diet and Microelement Supplementation in Pregnancy**

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### TABLE 6. Comorbidities in Pregnancy

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cardiovascular disorders:</td>
<td></td>
</tr>
<tr>
<td>Hypertension † (30% versus 9%)</td>
<td>24 hours blood pressure monitoring + methyldopa</td>
</tr>
<tr>
<td>(Coffin et al. (11) [2010])</td>
<td>if unstable → 24 hours urine collection</td>
</tr>
<tr>
<td>Preeclampsia †</td>
<td>+ labetalol or metoprolol and diuretics if necessarily*</td>
</tr>
<tr>
<td>2. Arrhythmia †</td>
<td>24 hours ECG + echocardiography</td>
</tr>
<tr>
<td></td>
<td>Exclude: hyperthyroidism, alcohol abuse</td>
</tr>
<tr>
<td>3. Diabetes mellitus: First and late second trimester oral glucose tolerance test (75 g, 0,1,2 hours)</td>
<td>If pump not available: fasting + 1 hour postprandial and →</td>
</tr>
<tr>
<td>If preeclaminal DM → insulin</td>
<td>Sotalol + strict fetal monitoring including NST weekly and EFW every 2 weeks</td>
</tr>
<tr>
<td>4. Anemia</td>
<td>Oral iron and folic acid →</td>
</tr>
<tr>
<td></td>
<td>Inpatient intravenous iron Hemoglobin ↓ 8 mg consider packed red blood cells transfusion</td>
</tr>
<tr>
<td>5. Thrombocytopenia</td>
<td>Oral steroids</td>
</tr>
<tr>
<td></td>
<td>Platelet count ↓ 100 × 10³ contraindication epidural anesthesia and ↓ 30 × 10³ ↑ risk of bleeding</td>
</tr>
<tr>
<td></td>
<td>Fresh frozen plasma, pooled platelets, and cryoprecipitate transfusions prior to cesarean section(8)</td>
</tr>
<tr>
<td>6. Liver failure/pregnancy cholestasis (9.1/1.000 pregnancies), associated with sudden intrauterine death ‡</td>
<td>Yellowning of the mucous membranes and skin itching of hands and feet (↑ at night)</td>
</tr>
<tr>
<td></td>
<td>↑ AST, ALT, bilirubin and bile acids Ursodeoxycholic acid derivatives up to 3 × 600 mg + close fetal monitoring</td>
</tr>
</tbody>
</table>

*After consultation with a cardiologist who is a specialist in the treatment of pregnant women, remember about previously mentioned interaction of CsA and nifedipine.
†See Heart Disease and Pregnancy (62) (2010).
‡If not responding to treatment, consider delivery after 36 weeks and intramuscular steroids.
such as LT recipients. In post-LT patients, we should be more concerned with the relative deterioration of platelet count, liver function, fetus growth, or fetal ultrasound Doppler impairment than the absolute values of each test.\(^{(33,60,63)}\)

The cesarean section in LT patients should be performed only based on obstetrical indications. It is important to encourage patients and their families to attend prenatal classes. In pregnancy at high risk of preterm birth, patients should be provided with care in the tertiary care unit with a specialized neonatology team and neonatal intensive care when available.

**EVERYDAY LIFE AND VACCINATION**

Recommendations for physical activity, work, travel, and sex life in uncomplicated pregnancies in this group of patients do not differ from recommendations for the general population. It also applies to preventive vaccination. If the woman was not vaccinated earlier, from the second trimester, immunization against seasonal influenza, hepatitis B, tetanus, diphtheria, rabies, and meningococcal should be considered.\(^{(64,65)}\) Studies have shown no pregnancy complications in the form of fetal growth restriction or preterm birth associated with vaccination.\(^{(66)}\)

**Puerperium**

Breastfeeding is recommended by the American Academy of Pediatrics as the sole diet of a newborn at least until the sixth month and should be gradually reduced along with the extension of the diet for the next 6 months.\(^{(67)}\) It reduces the incidence of allergies, celiac disease, infectious diseases, diarrhea, and colitis in children.

The exposure to immunosuppressants via breast milk is smaller than during the pregnancy. Only 0.1% of a steroid dose passes to breast milk. This is a much lower quantity than endogenously produced by the organism of a newborn\(^{(68)}\) and should not affect negatively its physical and psychomotor development.\(^{(69)}\) Moreover, in some studies, no detrimental effects of AZA on the newborns have been proven.\(^{(41)}\) Its levels in the diet and in the serum of 3-month infants are almost undetectable, and no increased susceptibility to infections or other complications has been found in neonates.\(^{(70)}\) A recent publication on 51 pregnancies in lupus patients receiving AZA and prednisone treatment suggests that those drugs may be continued while breastfeeding.\(^{(71)}\)

In the case of Tac and CsA, the first studies from the 1980s showed a significant passage of these drugs to breast milk. For CsA, they were even higher than in the mother’s blood, and for Tac, they reached approximately 50%. Further studies have shown that the dose of CsA passed from the breast milk to the infant was estimated at below 1 mg/kg, thus it was lower than those therapeutically used in children.\(^{(72)}\) For Tac, the serum concentrations of breast-fed infants decreased as compared to exposure during pregnancy, and they become undetectable after approximately 2 weeks.\(^{(73)}\)

Thus, the use of these drugs does not seem to be an absolute contraindication for breastfeeding. On the other hand, for MMF due to its confirmed teratogenic effects (miscarriages and fetal malformations), there are no studies describing its activity during breastfeed-ing in humans. Studies on rats have shown that it passes to the mother’s milk.\(^{(46)}\) The worldwide number of women breastfeeding after LT has been increasingly growing, reaching approximately 36% nowadays, compared with 1% observed in 1995.\(^{(70)}\)

Pregnancy in LT recipients is possible. If properly managed, the incidence of complications is acceptable, and the risk of organ deterioration or fetal malformation is insignificant. Critical factors for perinatal success are as follows: stable graft function, proper preparation for pregnancy, and cautious observation during its course. A young woman after transplant procedures should not be discouraged from pregnancy, but she should be carefully counseled toward its successful management.

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**REFERENCES**


1. The best time after transplantation when a patient should attempt conception should be
   a. after 1 month
   b. after 6 months
   c. after 1-2 years
   d. after 5 years

2. Breast feeding is allowed if the mother is taking which of the following immunosuppressants:
   a. cyclosporine
   b. tacrolimus
   c. azathioprine
   d. glucocorticoids
   e. all of the above

True or False

3. In general, pregnancy should be discouraged in patients who have undergone liver transplantation.

4. A pregnancy in a post-transplant patient with normal liver function has a 25% of ending in abortion

5. After liver transplant, oral contraceptive hormones should be discouraged, instead, transdermal hormones or intrauterine devices are advised for contraception.

6. Planned cesarean section is the preferred method of delivery for patients post liver transplant

7. Intrahepatic cholestasis of pregnancy is frequently seen in LT patients.

8. Mycophenolate mofetil should not be used as an immunosuppressant in post-transplant liver patients who wish to become pregnant.