

# Transplantation and Pregnancy

Pinar ERKAN UC<sup>1</sup>, Sermet SAGOL<sup>1</sup>

Izmir, Türkiye

## ABSTRACT

Transplantation is becoming increasingly widespread worldwide as a life-saving treatment for patients with end-stage organ failure. While the woman's quality of life improves rapidly after transplantation, the improvement of the endocrine system helps to regain fertility. The success of conception and successful pregnancy rates are quite low compared to the general population. Particular attention should be paid to obstetric complications such as hypertension, preeclampsia, fetal growth restriction, and preterm delivery during pregnancy. Ideally, preconception counseling should begin in the period before transplantation. Initiating contraception immediately after transplantation is ideal and long-acting reversible methods such as intrauterine devices and subcutaneous implants may be preferable. Factors that influence pregnancy outcomes in women undergoing organ transplantation include good general health within two years of transplantation, no evidence of organ rejection in the last year, stable graft conditions, absence of acute infections affecting the fetus, and adequate doses of immunosuppression drugs. However, factors that may adversely affect pregnancy include the etiology of the disease requiring transplantation, chronic allograft dysfunction, renal failure, cardiopulmonary diseases, hypertension, diabetes, obesity, and infections such as hepatitis B, hepatitis C, and Cytomegalovirus (CMV). Postponing pregnancy for at least 1 year after transplantation is very important to optimize pregnancy outcomes. Pregnancy in the early post-transplant period increases the risk of acute rejection, infection risk, and graft-related problems. In general, transplanted women can have successful pregnancies and live birth rates are above 70% on average. Although perinatal morbidity and mortality rates are high, most newborns are healthy and develop normally. Specific criteria such as pre-pregnancy serum creatinine levels and blood pressure control, as well as adherence to immunosuppressive therapy, significantly influence pregnancy success in transplant patients. In this review, optimizing pregnancy outcomes often involves addressing maternal and fetal risks, regular graft monitoring to detect potential complications such as organ rejection, and regulation of transplant medications to ensure safety and efficacy during pregnancy. Successful management relies on a multidisciplinary approach with contributions from obstetricians, neonatologists, nephrologists, hepatologists, and transplant surgeons.

**Keywords:** Kidney, Liver, Pregnancy, Transplantation

*Gynecol Obstet Reprod Med* 2024;30(1):62-74

<sup>1</sup> Department of Obstetrics and Gynecology, Ege University School of Medicine, Izmir, Turkey

Address of Correspondence: Pinar Erkan  
Department of Obstetrics and Gynecology,  
Ege University School of Medicine, 35100  
Bornova Izmir, Türkiye  
pnrerkan91@gmail.com

Submitted for Publication: 19.03.2024 Revised for Publication: 03.04.2024  
Accepted for Publication: 22.04.2024 Online Published: 24.04.2024

ORCID IDs of the authors: PE: 0000-0001-9322-6380  
SS: 0000-0002-4693-4090

QR Code	Access this article online
	Website: <a href="http://www.gorm.com.tr">www.gorm.com.tr</a> e-mail: <a href="mailto:info@gorm.com.tr">info@gorm.com.tr</a>
	DOI:10.21613/GORM.2023.1488

**How to cite this article:** Erkan P. and Sagol S. Transplantation And Pregnancy. *Gynecol Obstet Reprod Med.* 2024;30(1):62-74

 Copyright© 2024. Erkan et al. This article is distributed under a Creative Commons Attribution 4.0 International License.

## Introduction

Organ transplantation is increasingly becoming widespread worldwide due to being a life-saving and successful treatment method for patients with end-stage organ failure. Survival rates after solid organ transplantation have been rapidly improving since the first successful kidney transplant in 1954. The first successful pregnancy in a kidney transplant recipient occurred in 1958, with 23-year-old Edith Helm, who received a kidney from her twin brother, giving birth to a healthy baby boy weighing 3300 grams via cesarean section (1). From that time until today, successful pregnancies after kidney transplantation have been reported and continue to be reported, providing hope to transplant patients considering pregnancy.

Among transplant recipients, female patients hold a significant place. While female recipients accounted for 35% of liver transplant cases in 2011, this figure increased to 38% in 2021 (National data-OPTN. Organ Procurement and Transplantation Network) (2).

The ranking of organ transplant types in females in decreasing order is as follows: Kidney, Liver, Heart, Lung, Kidney-Pancreas, Pancreas, Intestine; whereas the ranking of patients who undergo transplantation and subsequently become pregnant is: Kidney, Liver, Kidney-Pancreas, Heart, Lung (3).

The rapid improvement of the endocrine system after transplantation enables fertility to return. However, both the likelihood of becoming pregnant and the success rates of pregnancies are much lower compared to the general population. Considering multiple risk factors for both the mother and the developing fetus, the pregnancy of a transplant recipient is considered high-risk. Transplant recipients considering pregnancy should be managed by a high-risk obstetrician in conjunction with the transplant team both before and during pregnancy.

Factors affecting pregnancy outcomes in transplant recipients (4).

- Good overall health within two years post-transplant.
- Absence of organ rejection in the past year.
- Stable graft condition.
- Absence of acute infections that could affect the fetus.
- Maintenance of immunosuppression with stable doses.
- Compliance of the woman with treatment and follow-up.
- Normal blood pressure or well-controlled blood pressure with a single medication.
- Normal graft ultrasound findings.

Co-morbid factors that may worsen pregnancy (4);

- Etiology of the disease requiring transplantation.
- Chronic allograft dysfunction.
- Renal failure.
- Cardiopulmonary diseases.
- Hypertension.
- Diabetes.
- Obesity.
- Maternal infections (Hepatitis B, Hepatitis C, and CMV).

#### ***Use of Immunosuppressants in Pregnant Transplant Recipients***

Complications that may arise with couples planning pregnancy after transplantation and the impact of immunosuppression on both the mother and the fetus should be discussed with the family as part of preconception counseling. The benefits of immunosuppressive therapy to maintain adequate graft function during pregnancy generally outweigh the potential risks associated with fetal effects. The use of stable doses of immunosuppressants before and during pregnancy is key to preventing problems in both the mother and the fetus. The immunosuppressive treatment regimen should be switched to medications that are less toxic to the fetus before conception. Corticosteroids, azathioprine, and calcineurin inhibitors (tacrolimus or cyclosporine) are commonly used medications during pregnancy. Mycophenolate mofetil is contraindicated during pregnancy (5)

Corticosteroids: Prednisolone and methylprednisolone, commonly used after transplantation, are converted to inactive metabolites by the enzyme 11  $\beta$  hydroxysteroid dehydrogenase in the placenta, resulting in minimal passage to the fetus. Studies have not shown evidence of teratogenicity, so the safe use of corticosteroids during pregnancy has been established (6).

Azathioprine: There is good safety data for its use during pregnancy. It has been associated with dose-dependent myelosuppression in the fetus, but maintaining the mother's white cell count  $>7500$  mm appears to minimize this risk. Lymphopenia, hypogammaglobulinemia, and thymic hypoplasia have been reported in children of mothers using azathioprine. However, these changes have been reported to reverse without long-term consequences after birth. Continuing azathioprine during pregnancy is safe when necessary in clinical practice (7).

Calcineurin inhibitors: Cyclosporine and tacrolimus are key molecules in the selection of immunosuppressive agents in pregnant women who are transplant recipients (8)

i. Cyclosporine: Easily crosses the placenta. Fetal blood concentrations vary between 30-60% of maternal concentrations. Current data show no increased risk of congenital malformations compared to unexposed patients. However, there is a moderate risk of intrauterine growth restriction (IUGR). Since suppression of hepatic cytochrome P450 enzymes during pregnancy may lead to changes in drug distribution, renal function, and liver clearance, cyclosporine levels should be monitored during pregnancy to prevent toxicity or maintain a low dose (9).

ii. Tacrolimus: Tacrolimus crosses the placenta, with fetal/newborn concentration approximately 50% of maternal concentration. Pregnancy outcomes with tacrolimus-based immunosuppression have shown a lower incidence of hypertension and preeclampsia compared to treatment with cyclosporine-based therapy. Nephrotoxicity and glucose intolerance may occur with tacrolimus-based treatments. Transient, unexplained hyperkalemia has been recorded in newborns, but this condition can be reversed without the need for treatment. The incidence of fetal malformations in pregnancies treated with tacrolimus is comparable to the general population, ranging from 4-5% (1). Overall, tacrolimus is considered safe during pregnancy, but its levels should be closely monitored by the transplant team. Target levels should be individualized based on the patient's history of rejection and concomitant conditions.

Mycophenolate Mofetil (MMF): Contraindicated during pregnancy. Risks include spontaneous abortion (49%), stillbirth (2%), and structural abnormalities (23%). Sifontis et al. reported teratogenic effects in 33 pregnancies involving various organ transplant recipients exposed to MMF in early preg-

nancy (10). High frequencies of malformations such as hypoplastic nails, short fifth fingers, microtia, and cleft lip/palate abnormalities have been observed. Other reported malformations include the absence of auditory canals, Tetralogy of Fallot, and total anomalous pulmonary venous return (11).

**Rapamycin Inhibitors:** Limited data are available regarding the effects of rapamycin (mTOR) inhibitors (e.g., sirolimus or everolimus) during pregnancy. The theoretical antiproliferative effect of these drugs may hinder fetal development. Successful pregnancies with mTOR inhibitors have been reported (12). However, these drugs continue to be contraindicated during pregnancy, and although a definitive interval has not been established, discontinuation of the drug before attempting pregnancy is recommended.

The likelihood of using tacrolimus, sirolimus, cyclosporine, azathioprine, and MMF during pregnancy is 60%, 27%, 20%, 16%, and 3%, respectively (13).

**Anti-thymocyte globulins and polyclonal immunoglobulins:** The use of these rejection-preventive agents during pregnancy has never been evaluated in clinical trials. Only a few case reports are available (5).

**Rituximab:** Like maternal IgG, rituximab can cross the placental barrier. When used during pregnancy, variable concentrations (30-120% of maternal concentration) have been detected in umbilical cord blood (5). Data on the use of rituximab in pregnant transplant recipients are not available in humans.

**Basiliximab:** Currently, no data are available in humans, and no teratogenic effects have been reported in animals (5).

### **Infections**

Predisposing factors leading to infection development in transplant recipients depend on epidemiological factors, including the recipient's immunosuppression status and the virulence of encountered organisms (4).

Whether an infection develops when encountering a pathogenic organism depends on the host's immune response and comorbidities. For instance, a patient with immunosuppressed vascular involvement diabetes is at greater risk for bacterial skin infections compared to a patient without immunosuppressed diabetes. If these risk factors are understood in each transplant patient, personalized preventive strategies (prophylaxis, vaccination) can be developed (4,14).

Risk factors for infection in transplant patients include (15):

- The type, dosage, and duration of immunosuppressive agents used.
- Technical difficulties during transplantation (e.g., blood, lymph, and urine accumulation), poor wound healing, and prolonged use of drainage catheters.
- Prolonged use of broad-spectrum antibiotics.

- Renal or hepatic dysfunction.
- The presence of an immunomodulatory infection such as CMV, Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).

Higher levels of immunosuppression may be required in the early post-transplant period, increasing susceptibility to infections such as CMV and herpes simplex virus (HSV) in women. Opportunistic infections are less common after the first year post-transplant. CMV infection is one of the infections that can result in serious consequences for both the mother and the fetus (16)

### **Contraceptive Methods**

Highly effective contraceptive methods should be recommended until appropriate conditions for pregnancy are achieved in women after transplantation.

Barrier methods provide the lowest theoretical risk in terms of systemic interactions and complications, but issues with compliance and overall effectiveness exist (17).

The use of hormonal contraceptive methods is generally recommended. However, in the early post-transplant period, hormonal contraceptive methods are not recommended due to potential interactions with calcineurin inhibitors (17). Following solid organ transplantation, a systematic review on the use of hormone-containing contraceptives (18) found that transplant recipients often experience chronic immunosuppression as a consequence of their condition, and treatment with immunosuppressive drugs poses potential concerns for the safety and efficacy of various contraceptive methods. While few high-quality data were identified, theoretical safety concerns exist among immune-suppressed transplant patients using combined oral contraceptives (COCs), progestin-only pills, medroxyprogesterone acetate (DMPA), and intrauterine devices (IUDs) (18).

Concerns exist about decreased contraceptive effectiveness due to drug metabolism as a result of using COCs or progestin-only pills in transplant patients receiving immunosuppressive treatment. Both oral contraceptives and many immunosuppressive drugs are metabolized by cytochrome P450 3A4 (CYP3A4) enzyme, which can affect the activity of this enzyme; hence drug interactions are possible (18) Induction of CYP3A4 by immunosuppressants such as glucocorticoids may lead to decreased efficacy of oral contraceptives. However, a study conducted in healthy women receiving oral glucocorticoids and COCs showed no change in contraceptive hormone levels. Conversely, inhibition of CYP3A4 by COCs can increase or decrease serum levels of concomitant immunosuppressive drugs (such as cyclosporine, tacrolimus, and sirolimus), potentially leading to toxicity or graft rejection (18).

All IUDs cause a local inflammatory reaction in the endometrium, and it has been suggested that macrophage activity plays a significant role in the destruction of sperm and oocytes. There is theoretical concern that the commonly used immunosuppressive agents in transplant patients may interfere with this inflammatory reaction; however, immunosuppressive agents are believed to have minimal effect on macrophage activity (19). Additionally, copper ions in copper IUDs and levonorgestrel in LNG-IUD play a significant role in the mechanism of action of these devices, and there is no known effect of immunosuppressive agents on copper ions or levonorgestrel (19).

Another theoretical concern is the use of DMPA. It is known that synthetic glucocorticoid steroids commonly used in patients after organ transplantation inhibit osteoblastic activity and increase bone resorption, thereby reducing bone formation (20). Fracture risk, along with bone loss, is the most common form of secondary osteoporosis, with fractures occurring in 30-50% of patients receiving chronic glucocorticoid therapy (21). The use of DMPA is associated with minor and usually reversible changes in bone mineral density, a marker for fracture risk, in postmenopausal women. However, it is unknown whether DMPA use exacerbates bone loss in organ transplant recipients treated with long-term glucocorticoid steroids or those already having osteoporosis.

Another theoretical concern regarding contraception in organ transplant recipients is that the use of combined oral contraceptives (COCs), combined hormonal patches, or vaginal rings may increase the risk of cardiovascular disease. According to the WHO, COCs should not be used in women with current or past deep vein thrombosis or pulmonary embolism. The risks of COC use outweigh the benefits in women with hypertension (22).

Hypertension can develop as a side effect of immunosuppressive therapy in organ transplant recipients. The WHO Medical Eligibility Criteria for Contraceptive Use states that for women with well-controlled hypertension, the theoretical or proven risks generally outweigh the benefits of COC use (22). However, the report of the ATS's consensus conference on reproduction and transplantation concluded that there is no information showing that COCs are associated with adverse outcomes among hypertensive transplant patients when hypertension is well controlled (4).

The use of oral therapies containing only progesterone for contraception is recommended in organ transplant recipients as their benefits outweigh their theoretical risks (23).

Although the American Transplantation Society does not recommend the use of IUDs as the first-line contraceptive treatment in this population, it remains a topic of debate as some reports suggest that IUDs may be effective in some patients (4).

All women starting treatment with mycophenolate mofetil (MMF) should receive contraceptive counseling before starting treatment and have a negative pregnancy test. Ideally, patients should use contraception for at least 4 weeks before starting MMF, during treatment, and for 12 weeks after discontinuing treatment.

### **Kidney Transplantation and Pregnancy**

These pregnancies should be managed jointly in tertiary centers with nephrologists, transplant surgeons, urologists, obstetricians, and pediatricians. Throughout pregnancy, the mother, fetus, and graft are at risk.

It is well known that end-stage renal disease has a devastating impact on quality of life. Patients often experience disruptions or complete upheaval of education, work, and family plans while dealing with their illnesses and treatment processes. Renal transplantation not only improves mortality but also increases opportunities to pursue personal and professional goals. Although successful pregnancies have been reported in patients with chronic kidney disease, women of childbearing age who are dialysis-dependent often cannot conceive. This is because uremia disrupts the hypothalamic-pituitary axis, often leading to irregular menstruation, anovulation, and infertility. Patients with chronic kidney disease have an average menopausal transition age of 4.5 years earlier than the general population (24).

Transplantation restores fertility and provides women with the opportunity to have children. However, negative maternal outcomes (such as gestational hypertension, preeclampsia, and proteinuria) are observed more frequently in pregnancies after transplantation, despite the restoration of fertility and the opportunity for women to have children (25).

Richman et al. reviewed the outcomes of renal transplantation pregnancies in more than 1,000 patients in North America, Australia, and Europe. The National Transplantation Pregnancy Registry (NTPR), established at Thomas Jefferson University in 1991, evaluated data from 1,356 pregnancies. Overall, the data indicate that pregnancies resulting in live births in kidney transplant recipients have a high chance of survival, but the risk of complications is higher compared to the general population (26).

Pregnancies in patients treated with calcineurin inhibitors have been shown to result in live births in 76-80% of cases, with spontaneous miscarriages occurring in 12-24% of pregnancies and the remaining resulting in induced miscarriages and stillbirths. Premature birth (<37 weeks) and low birth weight (<2500 g) have been among the most common complications affecting nearly half of the newborns. Preeclampsia (28-31%) and hypertension (52-68%) have often necessitated treatment in transplant patients, but very few cases have experienced rejection (1-3%) or graft loss during pregnancy (27).

Similar findings have been reported by the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry and the NTPR. ANZDATA reported a live birth rate of 76.9% among 577 pregnancies. Comparisons between 120 kidney transplant patients who had given birth and 120 who had not, based on transplant year, time since transplant, and pre-pregnancy creatinine levels, showed no difference in 20-year graft survival rates (28).

Data obtained from the United Kingdom organ transplant registry are consistent with other findings, reporting a live birth rate of 79%. At the beginning of pregnancy, at least 27% of registered patients in the UK had graft dysfunction and 69% had hypertension. Patients with normal pre-pregnancy graft function and blood pressure were found to have a higher likelihood of successful pregnancy (defined as live birth). Additionally, these patients had lower complication rates compared to those with deteriorating kidney function or developing hypertension (29).

Compared to NTPR data, the most common neonatal complications in the UK included early birth and low birth weight, reported in approximately 50% of cases. Risk factors for low birth weight, besides early birth, included pre-pregnancy serum creatinine levels  $>150 \mu\text{mol/L}$  (1.7 mg/dL) and the presence of hypertension requiring medication (29).

Patients with pre-pregnancy creatinine levels  $>150 \mu\text{mol/L}$  (1.7 mg/dL) exhibited a greater increase in baseline creatinine values compared to pregnant individuals with pre-pregnancy kidney function  $<150 \mu\text{mol/L}$  (1.7 mg/dL). However, the 2-year graft survival rate post-pregnancy was found to be 94%, which was similar to the non-pregnant control group (29).

### **Pregnancy Timing**

AST recommends delaying pregnancy for at least 1 year after kidney transplantation. The committee stated that the timing of pregnancy should be an individualized decision, taking into account factors such as the risk of acute rejection, infection, the potential need for potentially teratogenic drugs, and graft function. Before 2005, a waiting period of 2 years was advised, but advancements in immunosuppression and lower rates of early rejection have led the AST to become less restrictive. However, data on the optimal timing of pregnancy are insufficient (4,15,30).

Lessan-Pezeshki et al. found that in patients who became pregnant within 2 years after transplantation, the incidence of hypertension and preeclampsia during pregnancy was significantly higher compared to those who delayed pregnancy. However, the risk of preterm birth, low birth weight, early membrane rupture, infection, or graft dysfunction did not significantly change in patients who chose to become pregnant before 2 years (31).

Kuvacic et al. reported that in patients who became preg-

nant within less than 2 years after transplantation, the rates of spontaneous miscarriage and preterm birth were higher, but these differences were not significant (32).

Studies on the impact of timing on pregnancy outcomes are insufficient. Advising patients to wait for at least one year before becoming pregnant to confirm graft stability and minimize the risk of teratogenic infection may be the most reasonable practice until larger studies guiding recommendations become available.

Pregnancy Planning According to the 2005 AST Report (4).

- More than one year after kidney transplantation
- Optimal graft function, with serum creatinine level  $<1.5 \text{ mg/dL}$  (133 micromol/L) and absence of proteinuria or minimal proteinuria
- No rejection episodes in the past year
- Absence of acute or recent (but currently inactive) CMV infection. Patients with a recent history of CMV disease should wait at least six months, preferably one year, after infection before attempting pregnancy.
- Avoidance of teratogenic or fetotoxic drugs
- Good adherence to immunosuppressive treatment and stable drug levels

### **Obstetric Outcomes**

Most centers report live birth rates averaging  $>70\%$  (43-85%). The most common newborn complications are preterm birth and low birth weight. Among 19 centers providing data on fetal outcomes, only Pakistan and Mexico reported an incidence of preterm birth below 20%. Neonatal deaths and congenital anomalies are rare (33,34).

Sgro et al. reported an average gestational age at delivery of 36.5 weeks in the study group compared to 40.2 weeks in the control group. Babies born to transplant recipients (average  $2.54 \pm 0.67 \text{ kg}$ ) weighed less than those born to control group women (average  $3.59 \pm 0.53 \text{ kg}$ ) (35). Other single-center studies also reported similar data on average gestational age (35.2 weeks) and birth weight (2.4 kg) (36).

In a study at Ege University examining 52 post-renal transplant pregnancies, Hortu et al. reported a live birth rate of 82.6%. The average gestational age at delivery was  $36.35 \pm 2.36$  weeks. The preterm birth rate was 28.8%. They reported the mean birth weight as  $2664.58 \pm 613.99$  grams. They found a significant inverse correlation between birth weight and pre-pregnancy serum creatinine level (37).

Despite the high rates of prematurity and low birth weight, the majority of children born to women who underwent kidney transplantation have normal, healthy development (35,38). Long-term studies show that most children reach normal height and weight and generally perform well in school (35,38). Problems such as learning difficulties, developmental disorders, and hearing loss have been reported but are not

common (35). Children of kidney transplant recipients are followed until the age of 18, but little is known about their adulthood. A case report suggests that exposure to immunosuppressive agents in utero may increase the risk of autoimmune disorders later in life, but more data are needed to determine the risk (39).

Successful pregnancies among organ transplant recipients have been associated with pre-pregnancy serum creatinine levels of 1.5 mg/dL or higher, preterm birth, and low birth weight (34).

Ghanem et al. found that patients with proteinuria and hypertension had a higher likelihood of IUGR in fetuses, but Willis et al. did not find a relationship between kidney function and the risk of IUGR (40,41)

In a study by Bramham et al., it was reported that women with elevated pre-pregnancy creatinine levels (>1.4 mg/dL) and high diastolic blood pressure in the second/third trimester had approximately a 6-fold higher risk of poor fetal outcomes (stillbirth, abortion, neonatal death, <32 weeks gestation, and congenital anomalies) (27,42).

Therefore, pre-pregnancy creatinine level  $\leq 1.4$  mg/dL, absence of hypertension, and pre-pregnancy proteinuria <500 mg are associated with successful pregnancy outcomes. Additionally, younger maternal age and younger age at transplantation increase the likelihood of successful live births. Dialysis duration or history of transplantation from a living donor is not associated with successful pregnancy outcomes.

The risk of developing preeclampsia in renal transplant recipients is reported to be six times higher than in the normal population, with an incidence ranging from 24% to 38% (42). Low-dose aspirin use has been reported to reduce the risk of preeclampsia; however, in a study by Bramham et al., there was no difference in the risk of developing preeclampsia between pregnant women who used low-dose aspirin and those who did not (42).

Among 17 centers reporting preeclampsia data, preeclampsia incidence was found to be above 25% in 10 centers. Hypertension, urinary tract infection, and anemia were also among the most common complications (43).

The incidence of gestational diabetes in renal transplant recipients is reported to be 3-8%, which is not higher than the general population (42).

The risk of cesarean delivery in women who have had a renal transplant and become pregnant is higher compared to the general population, ranging from 43% to 64% (27,42). In most reports regarding the mode of delivery, it is stated that the transplanted kidney generally does not obstruct the birth canal, and vaginal delivery can usually be performed (44). Additionally, it is emphasized that cesarean delivery should be performed based on obstetric indications.

In a study by Bramham et al., based on data from the UK, the risk of cesarean delivery in renal transplant recipients was reported to be 5 times higher than in the general population, with fetal distress being the most commonly reported reason for cesarean delivery (42).

#### ***Maternal Morbidity and Graft Outcomes***

Single-center data suggests that women desiring pregnancy after kidney transplantation generally have excellent graft survival but are at a high risk of developing serious complications during pregnancy (45).

Five centers compared long-term outcomes in transplantation patients with a history of pregnancy to a control group of non-pregnant individuals and found no significant difference in graft function or survival. Fifteen-year survival rates were 85% in patients with a history of pregnancy and 79% in the control group. Graft survival at 15 years was 61-67% in the study groups and 58-69% in the control groups (46,47).

During a normal pregnancy, the glomerular filtration rate (GFR) increases by approximately 50%, and there is a significant decrease in serum creatinine levels. However, in pregnant transplant cases, the decrease in creatinine levels may be milder. In a study involving 101 recipients and 105 pregnancies, the mean serum creatinine level decreased from 1.33 mg/dL (118 micromol/L) before pregnancy to 1.18 mg/dL (104 micromol/L) in the first and second trimesters, then increased to 1.39 mg/dL (123 micromol/L) in the third trimester. However, 49% of patients did not experience a decrease in serum creatinine levels in the second trimester, and 38% experienced a decrease in graft function (defined as  $\geq 20\%$  increase in serum creatinine level from the lowest level during pregnancy). Preeclampsia was observed in 63% of cases with creatinine increase and acute rejection in 11% (48).

Serum creatinine levels should decrease in weeks 4-6 of pregnancy, remain stable in the second trimester, and rise to values close to pre-pregnancy levels in the third trimester. The absence of a decrease in the first trimester or an increase in serum creatinine level above the baseline pre-pregnancy value should be considered, and investigations, including ultrasound, proteinuria measurement, donor-specific antibodies, and possible allograft biopsy, should be planned (48).

Al Duraihimi et al. reported that patients with pre-pregnancy serum creatinine levels  $\geq 150$   $\mu\text{mol/L}$  (1.7 mg/dL) experienced more frequent deterioration in kidney function during pregnancy compared to those with normal initial creatinine levels (43).

In pregnant women with renal transplants, the risk of infection, especially bacterial urinary tract infections (UTIs) and acute pyelonephritis is higher due to the use of immunosuppressive drugs. UTI screening should be done at every visit with a urine dipstick and urine culture every 4 weeks. Asymptomatic bacteriuria should be treated with antibiotics

for 2 weeks and prophylactic treatment should be given for the remainder of the pregnancy. Evaluation for viral infections is also recommended (35).

While acute graft rejection after childbirth is not common in transplant patients, it may occur. Therefore, immunosuppressive therapy should be rapidly readjusted after childbirth. Pregnant patients, especially those with pre-existing hypertension, should be closely monitored for blood pressure, kidney function, proteinuria, and weight every 2-4 weeks, with more careful monitoring in the third trimester. Changes in antihypertensive agents may be necessary (49).

#### ***In conclusion;***

Although most renal transplant patients experience common side effects, they can still have successful pregnancies. Serious complications, such as preterm birth before 32 weeks, pregnancy loss in the first or second trimester, stillbirth, neonatal death, or congenital anomalies, are seen in approximately one-fourth of pregnant women (42).

Preeclampsia, induction of labor, and cesarean delivery rates are considerably higher compared to the general population. Additionally, small-for-gestational-age infants and preterm births are more common in renal transplant patients than in the general population. While studies have shown no increased risk of gestational diabetes in renal transplant patients, it is argued that current immunosuppressive treatments (such as tacrolimus and prednisolone) used in recent studies may predispose individuals to diabetes (42).

### **Liver Transplantation and Pregnancy**

Liver transplantation is a life-saving and successful treatment for acute liver failure and end-stage liver disease. Liver transplantation is particularly planned for patients with end-stage liver disease where life expectancy is expected to be over one year (50).

According to data from the Ministry of Health, between 2002 and 2023, a total of 74,704 organ transplants were performed in Turkey, of which 20,671 were liver transplants. In Turkey, the survival rate after liver transplantation is reported to be over 90% in the first year and over 75% in the fifth year. As of 2023, there were 2,600 patients awaiting liver transplantation in Turkey.

Reproductive-aged women with end-stage liver disease often experience serious complaints such as menstrual irregularities, amenorrhea, and infertility, affecting around 30-50% of them. Successful liver transplantation can restore menstruation as early as the first month, and 70-95% of recipients return to normal within a year. This likely indicates the restoration of fertility shortly after transplantation due to the rebalancing of sex hormones (13).

Various factors such as age, social status, side effects of

medications, and sexual dysfunction can reduce sexual activity in individuals with liver failure. Some of these factors improve after transplantation, but some patients continue to experience issues. Women recipients who fail to regain sexual function may experience problems with self-worth due to unemployment, ongoing health issues, changes in body image, and depression.

Since the first reported successful pregnancy after liver transplantation in 1978, case reports, case series, and data from the National Transplant Pregnancy Registries in the United States and the United Kingdom have been published. These records have shown that maternal and perinatal outcomes after liver transplantation are generally favorable. However, there is an increased risk of preeclampsia, preterm birth, and perinatal morbidity and mortality. Women after transplantation should be closely monitored for the potential adverse effects of immunosuppressive medications on the fetus and the liver during pregnancy (51).

#### ***Pregnancy Timing***

It is recommended to wait for at least one year, and in some cases up to 2 years, before planning pregnancy after transplantation. Among the reasons for this recommendation are the attainment of more predictable graft function, complete postoperative recovery, lower levels of immunosuppression requirement, reduced risk of opportunistic infections, and decreased likelihood of acute cellular rejection (27). However, the AST does not have a specific recommendation regarding the interval between liver transplantation and conception (4). When counseling patients, AST advises considering prognostic factors such as the absence of rejection episodes in the previous year, adequate and stable graft function, absence of acute infections, and stability of immunosuppressive dosage.

In 2009, the United States National Transplant Pregnancy Registry conducted a survey investigating pregnancy outcomes in transplant recipients, which showed that a transplant-pregnancy interval of more than 2 years was associated with decreased rates of low birth weight, rejection, and graft loss. Adverse perinatal outcomes were highest in women who became pregnant within 6 months after transplantation. In a single-center study, out of 38 pregnancies occurring within 12 months post-transplantation, only 1 successful live birth was reported. Consequently, the authors recommended delaying pregnancy for at least 2 years after transplantation (4).

Another single-center study involving 71 pregnancies reported no difference in live birth rates between the early group (conceiving within the first year) and the late group (conceiving >1 year after transplantation). However, the early group showed increased rates of prematurity, low birth weight, and acute cellular rejection reactions. Based on these findings, the authors recommended postponing pregnancy for at least one year after transplantation (52).

Patients at higher risk, such as those who have recently experienced acute cellular rejection or have irregular graft function or graft failure, are more likely to experience worse pregnancy outcomes (52). Therefore, delaying pregnancy in these patients and observing for 3-6 months before conception is appropriate. Careful counseling before pregnancy and obtaining multidisciplinary input from obstetric specialists during this period are advised.

### ***Maternal and Fetal Outcomes***

Generally, mortality in transplant-pregnant women is not different from the general population. Mortality rates during pregnancy and the postpartum period are less than 1% (53).

According to a meta-analysis evaluating 1496 pregnancies in 1073 liver transplant recipients, the live birth rate was reported as 86%, with abortion rates at 7-8% and stillbirth rates at 3-4% (13). In most studies, the stillbirth rate in liver transplant pregnancies is reported to be between 0-1.2%. However, some studies have reported rates as high as 12% (54).

There are numerous risk factors for stillbirth, including ethnicity, parity, previous stillbirth, infections, obesity, smoking, diabetes, hypertensive disorders, antepartum hemorrhage, placental abruption, IUGR, genetic disorders, and pregnancy cholestasis (23). The development of cholestasis during pregnancy is six times more common than in the general population; however, no adverse outcomes have been demonstrated (23). It has been shown that the risk of intrahepatic cholestasis in pregnancy significantly increases in patients with hepatitis C infection, but whether this risk persists after transplantation has yet to be determined (23). If cholestasis is suspected, monitoring with bile acids during pregnancy is recommended (23).

The frequency of obstetric complications is reported as 18% for hypertension, 13% for preeclampsia, and 7% for gestational diabetes in transplant recipients (13). The incidence of pregnancy-induced hypertension in some patient series ranges from 16% to 23%. The frequency of hypertension varies depending on the type of immunosuppression, with rates of 22-29% for corticosteroids, 63-73% for cyclosporine, and 47-54% for tacrolimus (54). Cyclosporine may be associated with higher rates of hypertension compared to tacrolimus.

Premature birth rates are increased in transplant pregnancies, with reported rates ranging from 14% to 53%. Prodromidou et al. reported a premature birth rate of 32% in a systematic review of 1079 pregnancies. The increased risk of prematurity may be associated with the increased frequency of obstetric complications such as preeclampsia in transplant cases (55).

Studies have shown that the incidence of IUGR is statistically more common in transplant recipients compared to the general population (56).

The frequency of congenital malformations does not differ from the general population (25).

The risk of congenital CMV infection is high in pregnancies occurring within the first 6 months after transplantation. Without support from perinatal HbIg and vaccination, the prenatal transmission of Hepatitis B is 80%, while the risk of vertical transmission of Hepatitis C is 7% (57).

Anemia is a common complication in transplant pregnancies and may arise secondary to physiological changes during pregnancy, the effects of immunosuppression, renal insufficiency, and iron deficiency.

Pregnancy is a physiological state of insulin resistance. Diabetogenic immunosuppressants, along with other risk factors, can lead to gestational diabetes. The rate of gestational diabetes in pregnant liver transplant recipients ranges from 0% to 11% (23). Therefore, early screening for diabetes and hypertension during pregnancy is important for all women.

Cesarean delivery rates in liver transplant pregnancies range from 20% to 63% in different publications (23). Vaginal delivery is not considered a contraindication.

### ***Graft Loss and Rejection***

The rates of graft rejection in pregnant liver transplant recipients can vary significantly, ranging from 0% to 20%. Postpartum graft rejection rates range from 3% to 12% (23). Rejection during pregnancy may be secondary to a combination of factors, such as the recipient discontinuing medication due to concerns about fetal side effects, reduction of immunosuppression, or the dilutional effect caused by increased plasma volume during pregnancy leading to decreased drug concentrations. Patients who develop acute rejection during pregnancy typically respond to corticosteroid therapy or the resumption or augmentation of immunosuppression.

In clinical monitoring, determining the cause of newly elevated liver enzyme abnormalities especially increases in transaminase levels, can be challenging in a pregnant transplant recipient. Initially, pre-pregnancy graft function and liver enzymes should be considered. It is also important to exclude viral causes. In cases of uncertainty, especially if management could be significantly impacted, liver biopsy may be considered.

Graft loss during pregnancy as a direct result of acute rejection is rare, but there have been reports of graft loss after delivery due to recurrent autoimmune hepatitis and chronic rejection (23).

Christopher et al. identified new kidney failure in 11% of pregnant liver transplant cohorts (52). Nagvi et al. reported that 25% of patients in their cohorts had creatinine levels >1.3 mg/dL during pregnancy (33). However, many studies have not found a significant decrease in kidney function during pregnancy (23).



Pre-delivery bleeding rates are reported to be similar to the general population (23). However, postpartum bleeding has been reported to be statistically more common in cases of transplant recipients compared to controls (8% vs. 3%, respectively) (23). This may be due to increased rates of cesarean delivery, immunosuppression-related thrombocytopenia, and coagulation disorders resulting from hypertensive disorders.

Pregnancy-related splenic artery aneurysm ruptures have also been described in transplant populations. Ideally, these aneurysms should be addressed before pregnancy (23).

Venous thromboembolism does not appear to be more common in transplant recipients compared to non-transplant individuals.

### **Pancreas Transplantation and Pregnancy**

Pregnancy is rare in patients who have undergone pancreas transplantation, but its management is complex. In the literature, 10 pregnancies, 2 surrogate pregnancies, and 8 live births have been reported. No birth defects were reported. Four pregnancies resulted in spontaneous abortions. Of those who were able to sustain their pregnancies beyond the second trimester, 2 ended in preterm births. Graft rejection was observed only in one patient in the postpartum fifth month. Although the number of reported cases is limited for conclusive interpretation, it can be inferred that in patients who have undergone pancreas transplantation alone, pregnancies can result in live births without serious complications. Graft rejection is also rarely observed (58).

Obstetric complications associated with solid organ transplantation include preeclampsia, gestational diabetes, preterm birth, and low birth weight.

### **Heart/Lung Transplantation and Pregnancy**

Lung transplantation is a valid treatment for selected patients with end-stage respiratory failure. Advances in this field have made it possible to improve life expectancy and quality of life. More than 43% of lung transplant patients are women of childbearing age. Ideally, the control of complications and achieving a stable clinical condition have made it possible for women who have undergone solid organ transplantation to have children. However, there are still ethical concerns (59).

There are limited studies concerning women who have undergone lung transplantation, typically involving single-center and small patient groups. According to the NTPR, a higher risk of complications (death, allograft rejection, and preterm birth) has been identified. Currently, there are no specific international recommendations for managing pregnancy in women who have undergone lung transplantation; only expert opinions are available (59).

Approximately 16,000 heart, lung, and heart-lung transplantations have been performed, and pregnancy is rare in patients who have undergone thoracic organ transplantation. Among 50 transplant recipients, 72 pregnancies were achieved, resulting in 48 live births. Studies on heart transplant recipients have shown that 69% of pregnancies resulted in live births, with 32% of them being premature and low birth weight infants. 9% ended in therapeutic abortion, and 17% ended in spontaneous abortion (60).

Maternal complications include hypertension (46%), acute graft rejection (21%), infection (11%), preeclampsia (10%), and gestational diabetes (4%) reported frequency (60).

Genetic counseling before pregnancy is mandatory in patients who have undergone heart transplantation secondary to genetic diseases such as mitochondrial myopathy, as such conditions can be inherited by the fetus.

Graft loss after lung transplantation has been reported to be 21% (60).

### **Management of Pregnant Transplant Patients**

- Pregnancy monitoring should be scheduled every 2-4 weeks during the first and second trimesters and every 1-2 weeks in later stages (4).
- The patient should measure her blood pressure daily, and hypertension should be aggressively treated as it is common in this patient group. ACE inhibitors and ARBs are contraindicated. Methyldopa can be used. Calcium channel blockers and Clonidine may also be preferred in necessary situations (61).
- Graft function should be monitored, and biopsy should be considered if rejection is suspected. Steroids are preferred in case of acute rejection (60).
- Pregestational diabetes is associated with congenital anomalies, and both pregestational and gestational diabetes are associated with fetal growth restriction, macrosomia, and fetal death. Glycemic control is important in early pregnancy to minimize potential harm to the fetus.
- If there are no obstetric indications, delivery should be planned at term (4).
- Vaginal delivery should be preferred unless there are obstetric indications for cesarean section. In the case of cesarean section, the location of the graft must be known to avoid damage to the graft (4).
- The cesarean section rate is 56.9% in kidney transplant patients and 44.6% in liver transplant patients (2).
- Antibiotic therapy should be administered for all surgical procedures. No specific local or general anesthetic agent has been reported as contraindicated (62).
- Patients who have undergone heart or heart/lung transplantation are at higher risk for pulmonary edema (60).
- In immunosuppressive therapy, the primary goal is to use

appropriate medications, measure their levels in the blood periodically, and thus avoid both excessive drug use and graft rejection or loss. Each trimester should be evaluated separately; for example, hyperemesis in the first trimester may affect drug absorption, while increased fetal metabolism of drugs in the third trimester may require reevaluation of dosage adjustments.

### ***Nutritional Recommendations for Transplant Pregnant Women***

Many immunosuppressive medications such as corticosteroids, tacrolimus, and cyclosporine have common metabolic and nutrition-related side effects. For example, corticosteroids can increase appetite and lead to weight gain. Therefore, the mother's nutrition should be appropriately monitored and modified during pregnancy to meet metabolic demands. To maximize complex carbohydrate intake and limit simple carbohydrate intake, carbohydrates should constitute 45% to 65% of total calorie intake (2).

- Fasting glucose should be maintained at <90 mg/dL and 2-hour postprandial glucose should be <120 mg/dL.
- Fats should contribute to 20-35% of total calorie intake, and trans fat intake should be minimized. Protein intake should be 1 g/kg/day.
- Consumption of fiber, adequate hydration, and folate supplementation should be provided.
- Calcium intake of 1000 mg/day and vitamin D intake of 0.25 mg/day should be ensured.
- Potassium levels should be monitored as hyperkalemia may develop in some patients (2).

### ***Lactation***

In the past, it was strongly advocated that solid organ recipients should not breastfeed. However, there has been a shift in international consensus towards the view that breastfeeding is not an absolute contraindication (63). While there is a lack of high-quality prospective studies, evidence regarding the safety of breastfeeding is slowly increasing. Patients should be informed about the potential risks of medication exposure and the benefits of breastfeeding.

Women receiving corticosteroid therapy may have small amounts of corticosteroids in breast milk. However, the effects on the infant at low doses are considered negligible. The American Academy of Pediatrics suggests that breastfeeding is relatively safe while using corticosteroids. A single dose of up to 20 mg of prednisolone per day is not expected to have adverse effects on the infant (63).

Low doses of azathioprine may be found in breast milk. Nevertheless, concerns remain regarding the long-term effects of medication exposure on immunosuppression, malignancy, and infant development. However, the harmful effects of azathioprine on newborns have not been demonstrated in many studies. The British Society for Rheumatology guidelines suggest that azathioprine is compatible with breastfeeding (64).

Drug levels in breast milk can vary significantly regardless of the mother's dose of cyclosporine. The American Academy of Pediatrics does not recommend breastfeeding with cyclosporine due to potential concerns about immunosuppression in the infant (65). Although long-term harmful effects have not been observed in newborns, breastfeeding is not recommended in clinical practice for patients taking cyclosporine.

New studies indicate that tacrolimus has very low absorption/effects on the infant and may therefore be compatible with breastfeeding (63).

The NTPR examined 98 solid organ transplant mothers who breastfed 126 of their children while using various immunosuppressive agents and regimens, and no specific problems related to breastfeeding were reported in the children (66).

There is very limited data on the safety of MMF and mTOR inhibitors during breastfeeding (23).

Drug levels in the mother's blood should be monitored while breastfeeding, and the decision to continue or discontinue breastfeeding should be based on the levels of the drugs.

While recent studies have been supportive of breastfeeding in solid organ transplant mothers, it remains a controversial topic that requires further research (2).

### ***Risks for Newborns Born to Transplant Pregnant Women (27)***

- Prematurity (up to 50% of cases), which is associated with neonatal death, cerebral palsy, deafness, learning difficulties, and low IQ.
- Fetal growth restriction.
- Immunosuppression (low Ig levels, low lymphocyte levels).
- Increased risk for congenital infections (toxoplasmosis, HBV, HCV, and CMV).
- Increased risk for autoimmune diseases.

### ***Postpartum Management***

- Due to changes in gastrointestinal absorption and motility during pregnancy, loss of fetal liver metabolism effects, maternal immune system restructuring, and potential for postpartum depression, the levels of immunosuppressive drugs should be monitored (2).
- Graft function should be monitored.

### ***Declarations***

*Competing interests:* The authors declare that they have no competing interests.

*Funding:* There is no financial support.

*Authors' contributions:* Conceptualization: PE, SS; Data Duration: PE, Investigation: PE, SS, Supervision: SS, Writing Original Draft: PE, Writing - Review and Editing: SS.

*Acknowledgment:* This study has been published on the

"Maternal-Fetal Medicine and Perinatology Society of Turkey" official website.

## References

- Shah S, Verma P. Overview of Pregnancy in Renal Transplant Patients. *Int J Nephrol*. 2016;2016:1-7. Doi: 10.1155/2016/4539342. PMID: 28042483, PMCID: PMC5155089.
- Deshpande NA, Coscia LA, Gomez-Lobo V, Moritz MJ, Armenti VT. Pregnancy after solid organ transplantation: a guide for obstetric management. *Rev Obstet Gynecol*. 2013;6(3-4):116-25. PMID: 24826201, PMCID: PMC4002187.
- Puoti F, Ricci A, Nanni-Costa A, Ricciardi W, Malorni W, Ortona E. Organ transplantation and gender differences: a paradigmatic example of intertwining between biological and sociocultural determinants. *Biol Sex Differ*. 2016;7:35. Doi: 10.1186/s13293-016-0088-4. PMID:27471591, PMCID: PMC4964018.
- McKay DB, Josephson MA, Armenti VT, August P, Coscia LA, Davis CL, et al. Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. *Am J Transplant*. 2005;5(7):1592-9. Doi: 10.1111/j.1600-6143.2005.00969.x. PMID: 15943616.
- Boulay H, Mazaud-Guittot S, Supervielle J, Chemouny JM, Dardier V, Lacroix A, et al. Maternal, foetal and child consequences of immunosuppressive drugs during pregnancy in women with organ transplant: a review. *Clin Kidney J*. 2021;14(8):1871-8. Doi: 10.1093/ckj/sfab049. PMID: 34345409.
- Blanford AT, Murphy BE. In vitro metabolism of prednisolone, dexamethasone, betamethasone, and cortisol by the human placenta. *Am J Obstet Gynecol*. 1977;127(3):264-7. Doi: 10.1016/0002-9378(77)90466-5. PMID: 835623.
- Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. *Arch Intern Med*. 2000;160(5):610-9. Doi: 10.1001/archinte.160.5.610. PMID: 10724046.
- Gong X, Li J, Yan J, Dai R, Liu L, Chen P, et al. Pregnancy outcomes in female patients exposed to cyclosporin-based versus tacrolimus-based immunosuppressive regimens after liver/kidney transplantation: A systematic review and meta-analysis. *J Clin Pharm Ther*. 2021;46(3):744-53. Doi: 10.1111/jcpt.13340. PMID:33386628.
- Unver Dogan N, Uysal II, Fazliogullari Z, Karabulut AK, Acar H. Investigation of developmental toxicity and teratogenicity of cyclosporine A, tacrolimus and their combinations with prednisolone. *Regul Toxicol Pharmacol*. 2016;77:213-22. Doi: 10.1016/j.yrtph.2016.03.010. PMID: 26993750.
- Sifontis NM, Coscia LA, Constantinescu S, Lavelanet AF, Moritz MJ, Armenti VT. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. *Transplantation*. 2006;82(12):1698-702. Doi: 10.1097/01.tp.0000252683.74584.29. PMID: 17198262.
- Merlob P, Stahl B, Klinger G. Tetrad of the possible mycophenolate mofetil embryopathy: a review. *Reprod Toxicol*. 2009;28(1):105-8. Doi: 10.1016/j.reprotox.2009.02.007. PMID: 19491002.
- Carta P, Caroti L, Zanazzi M. Pregnancy in a kidney transplant patient treated with everolimus. *Am J Kidney Dis*. 2012;60(2):329. Doi: 10.1053/j.ajkd.2012.05.012. PMID: 22805522.
- Marson EJ, Kamarajah SK, Dyson JK, White SA. Pregnancy outcomes in women with liver transplants: systematic review and meta-analysis. *HPB*. 2020;22(8):1102-11. Doi: 10.1016/j.hpb.2020.05.001. PMID: 32636057.
- Avery RK, Michaels M. Update on immunizations in solid organ transplant recipients: what clinicians need to know. *Am J Transplant*. 2008;8(1):9-14. Doi: 10.1111/j.1600-6143.2007.02051.x. PMID: 18093271.
- Fishman JA, Costa SF, Alexander BD. Infection in Kidney Transplant Recipients. In: *Kidney Transplantation - Principles and Practice*. Elsevier; 2019. p. 517-38. Doi: 10.1016/j.semnephrol.2007.03.006. PMID: 17616276.
- Azevedo LS, Pierrotti LC, Abdala E, Costa SF, Strabelli TMV, Campos SV, et al. Cytomegalovirus infection in transplant recipients. *Clinics*. 2015;70(7):515-23. Doi: 10.6061/clinics/2015(07)09. PMID: 26222822.
- Parhar KS, Gibson PS, Coffin CS. Pregnancy Following Liver Transplantation: Review of Outcomes and Recommendations for Management. *Canadian Journal of Gastroenterology*. 2012;26(9):621-6. Doi: 10.1155/2012/137129. PMID: 22993734, PMCID: PMC3441170.
- Paulen ME, Folger SG, Curtis KM, Jamieson DJ. Contraceptive use among solid organ transplant patients: a systematic review. *Contraception*. 2010;82(1):102-12. Doi: 10.1016/j.contraception.2010.02.007. PMID: 20682148.
- Estes CM, Westhoff C. Contraception for the transplant patient. *Semin Perinatol*. 2007;31(6):372-7. Doi: 10.1053/j.semperi.2007.09.007. PMID: 18063121.
- Kossov LR, Herbert CM, Wentz AC. Management of heart transplant recipients: guidelines for the obstetrician-gynecologist. *Am J Obstet Gynecol*. 1988;159(2):490-9. Doi: 10.1016/s0002-9378(88)80116-9. PMID: 3044118.
- Mazziotti G, Angeli A, Bilezikian JP, Canalis E, Giustina A. Glucocorticoid-induced osteoporosis: an update. *Trends Endocrinol Metab*. 2006;17(4):144-9. Doi: 10.1016/j.tem.2006.03.009. PMID: 16678739.
- Altshuler AL, Gaffield ME, Kiarie JN. The WHO's medical eligibility criteria for contraceptive use: 20 years of

- global guidance. *Curr Opin Obstet Gynecol.* 2015; 27(6): 451-9. Doi: 10.1097/GCO.0000000000000212. PMID: 26390246, PMCID: PMC5703409.
23. Rahim MN, Long L, Penna L, Williamson C, Kametas NA, Nicolaidis KH, et al. Pregnancy in Liver Transplantation. *Liver Transplantation.* 2020;26(4):564-81. Doi: 10.1002/lt.25717. PMID: 31950556.
  24. Holley JL, Schmidt RJ, Bender FH, Dumler F, Schiff M. Gynecologic and reproductive issues in women on dialysis. *Am J Kidney Dis.* 1997;29(5):685-90. Doi: 10.1016/s0272-6386(97)90120-7. PMID: 9159301.
  25. Huang H, Liu X, Lin X, Wu X, Qiu Y, Huang H. Successful pregnancies in post-kidney transplant couples: four case reports. *Front Immunol.* 2023;14:1215480. Doi: 10.3389/fimmu.2023.1215480. PMID: 37503336.
  26. Richman K, Gohh R. Pregnancy after renal transplantation: a review of registry and single-center practices and outcomes. *Nephrology Dialysis Transplantation.* 2012; 27(9):3428-34. Doi: 10.1093/ndt/gfs276. PMID: 22815546.
  27. Coscia LA, Constantinescu S, Moritz MJ, Frank A, Ramirez CB, Maley WL, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clin Transpl.* 2009;103-22. PMID: 20524279.
  28. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. *J Am Soc Nephrol.* 2009;20(11):2433-40. Doi: 10.1681/ASN.2008121241. PMID: 19797167, PMCID: PMC2799176.
  29. Sibanda N, Briggs JD, Davison JM, Johnson RJ, Rudge CJ. Pregnancy after organ transplantation: a report from the UK Transplant pregnancy registry. *Transplantation.* 2007;83(10):1301-7. Doi: 10.1097/01.tp.0000263357.44975.d0. PMID: 17519778.
  30. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. *Nephrol Dial Transplant.* 2002;17 Suppl 4:50-5. PMID: 12091650.
  31. Lessan-Pezeshki M. Pregnancy after renal transplantation: points to consider. *Nephrol Dial Transplant.* 2002;17(5): 703-7. Doi: 10.1093/ndt/17.5.703. PMID:1198 1050.
  32. Kuvacić I, Sprem M, Skrabljin S, Kalafatić D, Bubić-Filipi L, Milici D. Pregnancy outcome in renal transplant recipients. *Int J Gynaecol Obstet.* 2000;70(3):313-7. Doi: 10.1016/s0020-7292(00)00244-7. PMID: 10967164.
  33. Naqvi R, Noor H, Ambareen S, Khan H, Haider A, Jafri N, et al. Outcome of pregnancy in renal allograft recipients: SIUT experience. *Transplant Proc.* 2006;38(7): 2001-2. Doi: 10.1016/j.transproceed.2006.06.020. PMID: 16979978.
  34. Cruz Lemini MC, Ibarguengoitia Ochoa F, Villanueva González MA. Perinatal outcome following renal transplantation. *Int J Gynaecol Obstet.* 2007;96(2):76-9. Doi: 10.1016/j.ijgo.2006.11.006. PMID:17239381.
  35. Sgro MD, Barozzino T, Mirghani HM, Sermer M, Moscato L, Akoury H, et al. Pregnancy outcome post renal transplantation. *Teratology.* 2002;65(1):5-9. Doi: 10.1002/tera.1092. PMID: 11835226.
  36. Blanc AK, Wardlaw T. Monitoring low birth weight: an evaluation of international estimates and an updated estimation procedure. *Bull World Health Organ.* 2005;83 (3):178-85. PMID: 15798841, PMCID: PMC2624216.
  37. Hortu I, Arı SA, Akdemir A, Koroglu OA, Yılmaz M, Toz H, et al. Perinatal outcomes of renal transplant pregnancies: a 22-year experience at a single tertiary referral center. *J Matern Fetal Neonatal Med.* 2020;33(17):3028-34. Doi: 10.1080/14767058.2019.1639664. PMID:31288677.
  38. Areia A, Galvão A, Pais MSJ, Freitas L, Moura P. Outcome of pregnancy in renal allograft recipients. *Arch Gynecol Obstet.* 2009;279(3):273-7. Doi: 10.1007/s00404-008-0711-7. PMID: 18568355.
  39. Scott JR, Branch DW, Holman J. Autoimmune and pregnancy complications in the daughter of a kidney transplant patient. *Transplantation.* 2002;73(5):815-6. Doi: 10.1097/00007890-200203150-00028. PMID: 11907434.
  40. Ghanem ME, El-Baghdadi LA, Badawy AM, Bakr MA, Sobhe MA, Ghoneim MA. Pregnancy outcome after renal allograft transplantation: 15 years experience. *Eur J Obstet Gynecol Reprod Biol.* 2005;121(2):178-81. Doi: 10.1016/j.ejogrb.2004.11.035. PMID: 16009483.
  41. Willis FR, Findlay CA, Gorrie MJ, Watson MA, Wilkinson AG, Beattie TJ. Children of renal transplant recipient mothers. *J Paediatr Child Health.* 2000;36(3):230-5. Doi: 10.1046/j.1440-1754.2000.00500.x. PMID:108 49222.
  42. Bramham K, Nelson-Piercy C, Gao H, Pierce M, Bush N, Spark P, et al. Pregnancy in renal transplant recipients: a UK national cohort study. *Clin J Am Soc Nephrol.* 2013; 8(2):290-8. Doi: 10.2215/CJN.06170612PMID:230857 24, PMCID: PMC3562860.
  43. Al Duraihimh H, Ghamdi G, Moussa D, Shaheen F, Mohsen N, Sharma U, et al. Outcome of 234 pregnancies in 140 renal transplant recipients from five middle eastern countries. *Transplantation.* 2008;85(6):840-3. Doi: 10.1097/TP.0b013e318166ac45. PMID: 18360265.
  44. Ozlü T, Dönmez ME, Dağistan E, Tekçe H. Safe vaginal delivery in a renal transplant recipient: A case report. *J Turk Ger Gynecol Assoc.* 2014;15(2):125-7. Doi:10. 5152/jtgga.2014.45389. PMID: 24976780. PMCID: PMC 4072550.
  45. Schwarz A, Schmitt R, Einecke G, Keller F, Bode U, Haller H, et al. Graft function and pregnancy outcomes after kidney transplantation. *BMC Nephrol.* 2022;23(1): 27. Doi: 10.1186/s12882-022-02665-2. PMID: 35022021. PMCID: PMC8753888.

46. Rahamimov R, Ben-Haroush A, Wittenberg C, Mor E, Lustig S, Gafter U, et al. Pregnancy in renal transplant recipients: long-term effect on patient and graft survival. A single-center experience. *Transplantation*. 2006;81(5):660-4. Doi: 10.1097/01.tp.0000166912.60006.3d. PMID: 16534465.
47. Kim HW, Seok HJ, Kim TH, Han DJ, Yang WS, Park SK. The experience of pregnancy after renal transplantation: pregnancies even within postoperative 1 year may be tolerable. *Transplantation*. 2008;85(10):1412-9. Doi: 10.1097/TP.0b013e318170f8ed. PMID: 18497680.
48. Wiles K, Bramham K, Seed PT, Nelson-Piercy C, Lightstone L, Chappell LC. Serum Creatinine in Pregnancy: A Systematic Review. *Kidney Int Rep*. 2019;4(3):408-19. Doi: 10.1016/j.ekir.2018.10.015. PMID: 30899868, PMCID: PMC6409397.
49. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients. *Nephrol Dial Transplant*. 2002;17 Suppl 4:50-5. PMID: 12091650.
50. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines: Liver transplantation. *J Hepatol*. 2016;64(2):433-85. Doi: 10.1016/j.jhep.2015.10.006. PMID: 26597456.
51. Zullo F, Saccone G, Donnarumma L, Marino I, Guida M, Berghella V. Pregnancy after liver transplantation: a case series and review of the literature. *J Matern Fetal Neonatal Med*. 2021;34(19):3269-76. Doi: 10.1080/14767058.2019.1680632. PMID: 31635500.
52. Christopher V, Al-Chalabi T, Richardson PD, Muiesan P, Rela M, Heaton ND, et al. Pregnancy outcome after liver transplantation: a single-center experience of 71 pregnancies in 45 recipients. *Liver Transpl*. 2006;12(7):1138-43. Doi: 10.1002/lt.20810. PMID: 16799943.
53. Aydın Z, Güneş M. Pregnancy Following Kidney Transplantation. *Medical Bulletin of Haseki*. 2019;57(1):1-8. Doi: 10.4274/haseki.galenos.2018.4508.
54. Williamson C, Nana M, Poon L, Kupcinkas L, Painter R, Taliani G, et al. EASL Clinical Practice Guidelines on the management of liver diseases in pregnancy. *J Hepatol*. 2023;79(3):768-828. Doi: 10.1016/j.jhep.2023.03.006. PMID: 37394016.
55. Prodromidou A, Kostakis ID, Machairas N, Garoufalia Z, Stamopoulos P, Paspala A, et al. Pregnancy Outcomes After Liver Transplantation: A Systematic Review. *Transplant Proc*. 2019;51(2):446-9.
56. Cyganek A, Pietrzak B, Kociszewska-Najman B, Grzechocińska B, Songin T, Foroniewicz B, et al. Intrauterine Growth Restriction in Pregnant Renal and Liver Transplant Recipients: Risk Factors Assessment. *Transplant Proc*. 2014 Oct;46(8):2794-7.
57. Deshpande NA, James NT, Kucirka LM, Boyarsky BJ, Garonzik-Wang JM, Cameron AM, et al. Pregnancy outcomes of liver transplant recipients: a systematic review and meta-analysis. *Liver Transpl*. 2012;18(6):621-9. Doi: 10.1016/j.transproceed.2019.01.014. PMID: 30879563.
58. Gruessner AC, Gruessner RWG. The 2022 International Pancreas Transplant Registry Report-A Review. *Transplant Proc*. 2022 Sep;54(7):1918-43. Doi: 10.1016/j.transproceed.2022.03.059. PMID: 35970624.
59. Bry C, Hubert D, Reynaud-Gaubert M, Dromer C, Mal H, Roux A, et al. Pregnancy after lung and heart-lung transplantation: a French multicentre retrospective study of 39 pregnancies. *ERJ Open Res*. 2019;5(4). Doi: 10.1183/23120541.00254-2018. PMID: 31687369, PMCID: PMC6819984.
60. Armenti VT, Radomski JS, Moritz MJ, Gaughan WJ, Hecker WP, Lavelanet A, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clin Transpl*. 2004;103-14. PMID:16704142.
61. Cardonick E, Moritz M, Armenti V. Pregnancy in patients with organ transplantation: a review. *Obstet Gynecol Surv*. 2004;59(3):214-22. Doi:10.1097/01.ogx.0000115774.42302.d4. PMID: 15105711.
62. Armenti VT, Daller JA, Constantinescu S, Silva P, Radomski JS, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry: outcomes of pregnancy after transplantation. *Clin Transpl*. 2006;57-70. PMID: 18368705.
63. Constantinescu S, Pai A, Coscia LA, Davison JM, Moritz MJ, Armenti VT. Breast-feeding after transplantation. *Best Pract Res Clin Obstet Gynaecol*. 2014;28(8):1163-73. Doi: 10.1016/j.bpobgyn.2014.09.001. PMID:25271063.
64. Russell MD, Dey M, Flint J, Davie P, Allen A, Crossley A, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. *Rheumatology*. 2023;62(4):e48-88. Doi: 10.1093/rheumatology/keac551. PMID: 36318966 PMCID: PMC10070073.
65. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108(3):776-89. Doi: 10.1542/peds.108.3.776. PMID: 11533352.
66. Thiagarajan KMF, Arakali SR, Mealey KJ, Cardonick EH, Gaughan WJ, Davison JM, et al. Safety considerations: breastfeeding after transplant. *Prog Transplant*. 2013 Jun;23(2):137-46. Doi: 10.7182/pit2013803. PMID: 23782661.