

SOLID ORGAN (KIDNEY, LIVER, PANCREAS-KIDNEY, HEART, LUNG AND HEART-LUNG) TRANSPLANTATIONS AND PREGNANCY

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ABSTRACT

The frequency and variety of solid organ transplantation in reproductive-age women increases each year. Although most transplant-related pregnancies have been reported in women with kidney allografts, pregnancy is also possible in young women with other solid organ transplants including liver, pancreas-kidney, heart, lung and heart-lung transplants. Most of these pregnancies have resulted in a successfull outcome; however, for optimal maternal and neonatal outcomes, a multidisciplinary approach including careful follow-ups of the obstetrician and transplant team is essential. This article reviews and discusses preconceptional counselling, graft rejection and dysfunction during pregnancy, safety of immunosuppressive medications with regard to fetus, and perinatal risks and pregnancy management for women with various solid organ transplants, taking into consideration previous published reports, especially The National Transplantation Pregnancy Registry (NTPR)'s.

Keywords: Solid Organ Transplantation, Pregnancy, Complications

SOLİD ORGAN (BÖBREK, KARACİĞER, PANKREAS-BÖBREK, KALP, AKCİĞER VE KALP-AKCİĞER) TRANSPLANTASYONU VE GEBELİK

ÖZET

Reprodüktif çağdaki kadınlarda solid organ transplantasyonu sıklığı ve çeşitliliği her geçen yıl artmaktadır. Transplantla ilişkili gebeliklerin çoğu böbrek allogreftli kadınlarda bildirilmesine rağmen; karaciğer, pankreas-böbrek, kalp, akciğer ve kalp-akciğer transplantları gibi diğer solid organ transplantlı genç kadınlarda da gebelik mümkündür. Bu gebeliklerin çoğu başarılı bir akibetle sonuçlanmaktadır; bununla birlikte, optimal maternal ve neonatal sonuç için, obstetrisyen ve transplant ekibinin dikkatli takiplerini içeren multidisipliner bir yaklaşım esastır. Bu çalışma National Transplantation Pregnancy Registry (NTPR)'ninkiler başta olmak üzere daha önce yayınlanmış raporları göz önünde bulundurarak, çeşitli solid organ transplantlı kadınlarda prekonsepsiyonel danışmanlık, gebelik sırasında greft rejeksiyonu ve disfonksiyonu, immunsupresif tedavinin fetus açısından güvenilirliği ve perinatal riskler ve gebelik yönetimini gözden geçirmekte ve tartışmaktadır.

Anahtar Kelimeler: Solid Organ Transplantasyonu, Gebelik, Komplikasyonlar

INTRODUCTION

Organ transplantation is a life-saving procedure for those with end stage disease. Menstruation will often return after transplantation as organ function normalizes¹⁻⁴.

İletişim Bilgileri:

Yusuf Yildirim, M.D. Aegean Obstetrics and Gynecology Training and Research Hospital, Obstetrics and Gynecology, Izmir, Türkiye e-mail: dr.yusufyildirim@yahoo.com.tr For example; in a previous prospective controlled study we compared 28 renal transplant recipients and 30 healthy women, with respect to hormonal and menstrual characteristics. The study showed that there

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was no statistically significant difference in serum FSH, LH, and E2 levels between the transplant and control groups¹.

Since the first documented pregnancy in a transplant recipient occurred in 1958, successful pregnancies have been reported in female recipients of kidney, liver, pancreas-kidney, heart, and lung transplants²⁻¹¹. However, many uncertainties still exist including the risks that pregnancy presents to the graft, the patient herself and to the fetus. This review has focused on preconceptional counselling, graft rejection and dysfunction, immunosuppressive medications with regard to pregnancy safety and perinatal risks and pregnancy management for women with various organ transplants.

II. PRECONCEPTIONAL COUNSELLING (Table I)

Optimal timing of pregnancy

How to counsel a woman who has undergone a transplant about when to become pregnant is difficult because of limited clinical experience regarding this topic. Although gonadal dysfunction usually resolves by 6 months after successful transplantation⁴, patients are generally advised to wait 2 years after transplantation to become pregnant. This time is based on the timeframe to establish stable graft function maintenance on immunosuppression. It is also expected that transplant recipients will have completed postoperative treatment of opportunistic infections by this time. The initial recommendation to wait 2 years was based on rejection risk, but more recent and potent immunosuppressive strategies have greatly decreased rejection rates in the post-transplant year. If the patient has adequate and stable

graft function, is at low risk for opportunistic infections and is not taking teratogenic medications, it may be that pregnancy can be attempted only one year after transplantation without concern of increased risks⁵.

Much of the experience in organ from transplantation comes the renal transplant population. Pregnancy is not contraindicated in renal transplant recipient who have stable renal function. The most important factor affecting pregnancy outcomes is the length of time from transplantation to conception, and women desiring a pregnancy should wait at least 2 years to conceive⁶. Stable renal function (serum creatinine level less than 2 mg/dl), no recent episodes of acute rejection, a systemic arterial blood pressure of 140/90 mm Hg or less, proteinuria less than 500 mg/day, and normal allograft ultrasound results are also recommended⁷. Poorer outcomes are observed in women who have graft dysfunction or hypertension before conception. The normal increase in glomerular filtration rate (GFR) still occurs in pregnant women with renal transplants. In general, renal function during pregnancy correlates within the renal function before pregnancy⁸.

Since the first liver transplantation in 1978, successful pregnancies have been reported for many liver transplant recipients. For liver transplant recipients, acute cytomegalovirus (CMV) infection usually occurs within 6 months after transplantation, coinciding with the period of maximal immunosuppression after transplantation. It is therefore recommended that a liver transplant recipient should delay conception at least 6 months after transplantation⁹.

Table I. Preconceptional Counseling Issues

Contraception and counselling optimal timing for pregnancy
Continuation of immunosuppressant medication
Folic acid* and calcium# supplementations
Performing rubella and varicella vacciniation, if required
Cervical cytology for screening cervical cancer
Screening and treating anemia and infections
*: 400 microgram/day

^{# 1000} mg /day



Contraception

There are limited data on appropriate contraception following transplantation, including barrier methods, the intrauterine device, and oral contraceptives. The literature cites many theoretical complications for the hormonal approaches, and generally the transplant community has favored barrier methods, among the least effective of modern approaches¹⁰. contraceptive Oral contraceptives are effective, but are generally recommended in normotensive women and are to be avoided in hepatic allograft patients because of the possible negative hepatic effects of these medications¹¹. Also oral contraceptives can potentially affect certain medications.

The optimal contraceptive agent to use after transplantation depends on balancing the risks and benefits of each of possible contraceptive method.

Pre-pregnancy folic acid supplementation

To reduce the occurrence of open neural tube defects, 1 to 2 months before conception at least 400 microgram/day folic acid supplementation should be recommended¹².

Detecting infections and asymptomatic bacteriuria

Transplant patients are at increased risk for CMV or herpes simplex virus (HSV), toxoplasmosis, and hepatitis B and C infections due to their immunosuppressed state. Up to 40 % of pregnant transplant patients have urinary tract infections. Pregnant women can have asymptomatic bacteruria, therefore each trimester a urine culture should be checked rather than screening patients by symptoms. It is important to prevent or treat any infections and to use a low threshold for initiating antiobiotic therapy¹³.

Screening for cervical cancer

Human papillomavirus (HPV) and cervical neoplasia rates are higher in immunocompromised and transplant recipients, therefore patients should be screened during prenetal care with cervical cytology¹⁴.

Vaccination

An immunization history of the nonpregnant transplant patient is essential. Laboratory evaluations for CMV, rubella, varicella, HSV, toxoplasmosis, human immundeficiency virus (HIV) and hepatitis panel should be performed before pregnancy. Vaccination of an immunosuppressed patient using live virus vaccines could result in systemic sepsis and Therefore rubella and death. varicella vaccines should be administered to women of childbearing before organ age transplantation^{15,16}.

III. PERINATAL RISK AND PREGNANCY MANAGEMENT

Successful management of the pregnant transplant patient requires a cooperative effort between the obstetrician and transplant team. Various pregnancy complications are possible in patients with transplantation (Table II). Concerning the pregnancy, the major goals are to optimize maternal health including graft function, to maintain a normal metabolic minimize complications environment, associated with preterm delivery and birth defect and manage hypertensive complications especially pre-eclampsia and ensure adequate fetal growth. All patients require close scrutiny including more frequent prenatal visits.

Kidney Transplantation

Hypertension or preeclampsia develops in 25-30% of patients with kidney transplants. Preeclampsia can be difficult to diagnose, because in the third trimester, 40% of patients with a renal transplant have a transient increase in proteinuria¹⁷⁻²⁰.

It is reported that abnormal glucose tolerance test results occur in up to 13.8% of pregnant renal transplant recipients whose immunosuppressive therapy consists of corticosteroids^{21,22}. An early glucose challenge is recommended in the first trimester and again between 24 and 28 weeks if this early screen is negative^{9,11}.

Table II. Pregnancy complications

Maternal complications
Chronic Hypertension
Preeclampsia/Superimposed Preeclampsia
Infection
Diabetes
Graft rejection and dysfunction
Fetal complications
Fetal growth restriction
Preterm labor
PROM
Low birthweight
PROM: Preterm rupture of membranes

The spontaneous abortion rate is not higher than in the general population²³. On the other hand, pregnancies in women with renal transplants can also be complicated by anemia²⁴.

Other perinatal complications include preterm delivery in 45% to 60% of patients, preterm premature rupture of membranes, and intrauterine growth restriction in 20% of pregnancies⁵. Over 50% of babies born to kidney transplant recipients are delivered at than 37 weeks gestation¹⁷. The less consequences of decreased gestational age, particularly under 34 weeks of gestation include neonatal death, cerebral palsy, blindness, deafness and learning disabilities. Also low birth weight may be associated with increased hypertension, diabetes and coronary artery disease in adulthood²⁵. Fetal growth ultrasounds during pregnancy are important because medications and underlying maternal medical conditions can affect fetal growth.

Despite its pelvic location, the transplanted kidney rarely causes dystocia and is not injured during vaginal delivery¹⁸. Cesarean deliveries are not required, such surgical deliveries are reserved for obstetric indications¹⁷.

In a previous study we analyzed 20 pregnacies in 17 renal transplant patients. There were 16 preterm or term live deliveries, 3 therapeutic abortions, and 1 spontaneous abortion. The mean gestational age at delivery

was 37.8±2.1 weeks (range, 28-41 weeks) and the prematurity rate was 31.25%. The mean birth weight was 2950±719 g (range, 920-4230 g), and there were 3 newborns (18.75%) with low birth weight. One newborn (6.25%) was small for gestational age and there was 1 neonatal death (6.25%). No stillbirths or congenital abnormalities were noted. The complications following maternal were observed: 6 cases of preeclampsia (30%), 4 of proteinuria greater than 500 mg/day (20%), 3 of worsening hypertension (15%), 2 of pyelonephritis (10%), and 1 of gestational diabetes mellitus (5%). There were no episodes of graft failure or rejection².

Liver Transplantation

Liver recipients are also at high risk for hypertension, preeclampsia, fetal growth restriction, anemia, infection and preterm labor²⁶. Severe preeclampsia marked by hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome is difficult to distinguish from rejection or progression of underlying liver disease, especially hepatitis associated with hepatitis C^{27} . On the other hand, the rate of maternal-fetal hepatitis C transmission is unknown in liver transplant recipients and requires additional prospective analysis.

Renal dysfunction had the strongest association with adverse pregnancy outcome in liver allograft recipients¹³.



According to the National Transplant Pregnancy Registry (NTRP)'s review the mean gestational age at delivery was 37 weeks and the mean birth weight was 2.705 gms²⁸.

Pancreas-Kidney Transplantation

NTPR reported 56 post-transplant pregnancies with 58 outcomes. Only one recipient reported gestational diabetes; regular insulin was started at 24 weeks but was discontinued postpartum. According to the NTPR report transplant to conception interval was 3.7 years. The mean gestational age was 34 weeks and mean birth weight was 2.096 g. Thirty-four percent of pregnancies were complicated by preeclampsia²⁸.

Heart, Lung, and Heart-Lung Transplantation

As cardiac transplantation has become an accepted treatment for end-stage cardiac disease, a growing number of women of childbearing age are receiving this therapy. Pregnancy is associated with significant haemodynamic demands. Blood volume increases 40% and cardiac output by 30%. If pre-pregnancy cardiac function is normal, the transplanted heart is generally able to adjust to these demands²⁹.

According to the NTPR report the mean gestational age was 37 weeks for heart recipients and 35 weeks for the lung recipients. Preeclampsia complicated 10% of heart transplant pregnancies and 13% of lung transplant pregnancies. Compared to pregnancy outcomes in other solid-organ recipients, female lung recipients had a higher risk of premature delivery such as 63%, correspondingly lower birth weights (2.285 gms), a high risk of rejection episodes with 27% during pregnancy, and may have a higher long term mortality²⁸.

IV. GRAFT REJECTION AND DYSFUNCTION

It is suggested that pregnancy is an immunosuppressed state but evidence shows pregnant women do not have diminished systemic immunity³⁰. Inappropriate reduction

in immunosuppression during pregnancy will lead to rejection of the transplanted organ⁵.

Kidney transplantation

Overall, the literature suggests that pregnancy does not have an adverse effect on the renal allograft if renal function is well preserved before pregnancy³¹. Serious renal allograft rejection occurs in approximately 9% of pregnancies, an incidence that is no greater than that seen in non-pregnant women³². Women with a serum creatinine level greater than or equal to 2.5 mg/dl are three times more likely to experience graft loss than those with a serum creatinine level less than 1.5 mg/dl³³. Rejection may be difficult to detect during pregnancy, particularly in renal and liver transplant recipients. Without a renal biopsy, rejection cannot be distinguished from acute pyelonephritis, preeclampsia, recurrent glomerulopathy or nephrotoxicity 32 . If there is no improvement in renal function after 3 days of hospitalization, a renal biopsy is often required to distinguish acute rejection³¹. Rejection should be suspected if there is fever, increased weight gain, decreased urine volume, graft tenderness, rapid rise in serum creatinin levels; BUN/creatinin < 20.cyclosporine levels < 150 mg/ml, renal biopsy findings of endovasculitis, tubulitis, or glomerulitis. Termination of pregnancy does not guarantee improvement in or stabilization of renal function. If renal function deteriorates without a concomitant rise in blood pressure, the prognosis for successful pregnancy is $good^{32}$.

Liver transplantation

If the graft function is stable, pregnancies are well tolerated in liver transplant recipients. Pregnancy does not appear to alter hepatic allograft function. According to the NTRP's review, the rejection rate during pregnancy was 8% and there were no neonatal deaths in liver transplant recipients²⁸.

Mild to moderate elevation of liver enzymes is common in liver recipients and could represent the baseline before conception. New elevations of liver enzymes or bilirubin could signify allograft rejection and require investigation. Liver Doppler ultrasound to



exclude anatomic sources of graft dysfunction is useful, and liver biopsy to diagnose allograft rejection is not contraindicated in pregnancy¹³.

Pancreas-Kidney Transplantation

Pregnancies following pancreas-kidney transplantation are well-tolerated with respect to graft function. Rejections during pregnancy occurred in 6% of the patients. There were 6 graft losses within 2 years postpartum among the pancreas-kidney recipients. Three of them lost kidney function, one lost pancreas function, and 2 recipients lost both pancreas and kidney function²⁸.

Heart, Lung, and Heart-Lung Transplantation

Maternal cardiac graft rejection ranges from 20% to 26%, but the mortality rate for pregnant heart transplant recipients is not higher than for non pregnant women³⁴. Lung transplant recipients may experience a higher incidence of rejection during pregnancy than recipients of other solid organs, for reasons that are not yet known³⁵. Data are still limited for lung transplant patient so there are no well-defined recommendations for these patients.

According to the NTPR report there were no maternal graft losses within 2 years of pregnancy in the female heart recipients reported to NTPR, but maternal graft losses within 2 years of pregnancy in the female lung recipients reported to NTPR was 21%²⁸.

V. TOXIC EFFECTS ON THE FETUS OF IMMUNOSUPRESSIVE AGENTS

Immunosuppressive agents are necessary to maintain graft function and maternal survival. No specific combination of agents is superior; a woman can continue on the same immunosuppressive regimen during her pregnancy³⁶. A combination of various agents allows for synergistic effects and decreases the risk of drug toxicities.

Most immunosuppressive agents are United States Food and Drug Administration (FDA) Category C for safety which suggests the use of the agent only if potential benefit justifies potential fetal risk (Table 3).

It has been proven that all of the drugs readily cross the human placenta and diffuse to the Although many studies fetus. have consistently have found there is no increased prevalence of human malformations in newborns in transplant recipients when compared with a background malformation risk of 2-3% for all gravidas^{37-41,} there is little experience with newer drugs³⁹. Exposure of infants to immunosuppressive medications in utero might increase the child's risk for autoimmune disease later in life⁴⁰.

A-Corticosteroids

Corticosteroids prevent interleukin (IL)-1 and IL-6 production by macrophages and inhibit all stages of T-cell activation. This agent is used for induction. maintenance of immunosuppression, and acute rejection. Corticosteroids are the only immunosuppressive drugs that are classified as FDA category B agents. Most transplant patients are maintained on long term, high dose corticosteroids (>30 mg/day).

Adverse effects of steroid therapy include Cushing's disease, bone disease (eg. osteoporosis, avascular necrosis), cataracts, glucose intolerance, infections. hyperlipidemia, peptic ulcer, diabetes, and disturbances³⁶. psychiatric Calcium supplementation (1000 mg /day) has been shown to be effective in improving bone mineral density in these women⁴². Researches have also reported increased occurrences of preterm labor and premature rupture of membranes in women with transplants, possibly due to long term steroid use, which is postulated to weaken amniotic membrane integrity³².

Steroid withdrawal has been used as a strategy to avoid adverse steroid effects in transplantation patients. After tacrolimus became available, protocols with this drug showed that withdrawal of steroids after 6 months was successful 80% of the time. Recently, a follow-up study of 100 patients in Denmark who underwent transplantation on steroid-free protocols showed a 1-year graft survival rate of 97% and a 4-year rate of $82\%^{43}$.



Table 3. FDA category	of Immunosuppress	ive Agents Used in	Transplant Recipients

mmunosuppressive Agents	FDA category
Corticosteroids	В
СуА	С
Tacrolimus (FK 506)	С
AZA	D
MMF	С
Sirolimus	С
ATG	С
Muromonab-CD3	С
Daclizumab	С

FDA: Food and Drug Administration (United States) CyA: Cyclosporine-A AZA: Azathioprine MMF: Mycophenolate mofetil ATG: Antithymocyte globulin

B-Calcineurin inhibitors

1. Cyclosporin A (CyA)

CyA is a polypeptide of 11 amino acids of fungal origin and is active against helper T cells, preventing the production of IL-2 via calcineurin inhibition (binds to cyclophilin protein). This agent is used for induction and maintenance immunosuppression.

Multiple drug interactions are possible, primarily with agents affecting the cytochrome P-450 system. Shown toxicities of CyA therapy include nephrotoxicity, hypertension, hypertrichosis, tremor and hyperlipidemia. Therefore, CyA levels (fasting) should be monitored at least monthly. Hypertrichosis and hirsutism can be alleviated by switching from CvA to tacrolimus, provided the patient is carefully monitored.

The fetus exposed to CyA is at risk for intrauterine growth restriction, but the risk from the medication itself is difficult to distinguish from the risk associated with the underlying medical conditions in this population of patients.

2. Tacrolimus

Tacrolimus is a macrolide antibiotic and is active against helper T cells, preventing the production of IL-2 via calcineurin inhibition (binds to tacrolimus-binding protein instead of cyclophilin protein). It has been proven to be a more potent immunosuppressive agent. This agent is used for maintenance immunosuppression and for rescue therapy in patients with refractory rejection under cyclosporine-based therapy. Tacrolimus can not be used with CyA because of synergistic nephrotoxicity. Adverse effects include nephrotoxicity, neurotoxicity, glucose intolerance, and QT prolongation (rare). Tacrolimus causes fewer cosmetic effects than CyA, but it can cause reversible alopecia.

Studies show maternal fetal toxicities to be dose-dependent⁴⁴. There is an increased prevalence of maternal nephrotoxicity that is lower than in women treated with CyA⁴⁵. A fetal echocardiogram between 20 and 22 weeks should be considered for patients on tacrolimus because cases of cardiomyopathy in newborns have been reported⁴⁶. Other neonatal adverse effects include a higher incidence of diabetes and transient hyperkalemia³⁶.



C-Purine metabolism inhibitors

1. Azathioprine (AZA)

AZA is a derivative of 6-mercaptopurine. It functions as an antimetabolite to decrease DNA and RNA synthesis and is used for the maintenance of immunosuppression.

Adverse effects include leukopenia, thrombocytopenia, hepatitis, cholestasis, and alopecia. Myelosuppression can improve with drug discontinuation.

Teratogenicity has been noted in animal studies and AZA is an FDA Category D drug. Increased rates of leucopenia, thrombocytopenia, and anemia have been reported in infants. During organogenesis, the fetus may be protected from any adverse effect of AZA because it lacks the enzyme, inosinate pyrophosphorylase, necessary to convert the drug to its active metabolite⁴⁴. Overall, no clear pattern of congenital anomalies has been identified in fetuses exposed to AZA in utero. With the availability of newer agents, azothioprine use has decreased markedly.

2. Mycophenolate Mofetil (MMF)

inhibits the MMF enzyme inosine monophosphate dehydrogenase (required for guanosine synthesis) and impairs B- and Tcell proliferation, sparing other rapidly dividing cells (because of the presence of guanosine salvage pathways in other cells). This agent is used for maintenance immunosuppression and chronic rejection. This drug is more selective than AZA seems to be synergistic with CyA and tacrolimus, and may be the first drug that is effective in reducing the rate of chronic rejection. Adverse effects include nausea, vomiting, diarrhoea, leukopenia, anemia. and thrombocytopenia³⁶.

There are no epidemiologic studies currently available on the safety of this drug in pregnancy. Because there is no safety margin based on reproductive toxicology studies in animals, there is a possibility of increased risk in humans. Recently a case report of major congenital malformations associated with in utero exposure to MMF has raised interest³⁹.

D-Sirolimus

Sirolimus is macrolide that inhibits T cell proliferation by cytokine inhibition without affecting calcineurin inhibition. This agent is used for the maintenance of immunosuppression and chronic rejection. Sirolimus can be used concomitantly with tacrolimus, CyA, or MMF. Adverse effects include hyperkalemia, hypomagnesemia, hyperlipidemia, leukopenia, anemia, impaired wound healing, and joint pain. Multiple drug interactions are possible, especially because of the extremely long half-life.

Sirolimus is classified as an FDA Category C agent in pregnancy, but no definitive clinical pregnancy outcome data are available. Delayed skeletal ossification and decreased fetal weight in animal studies have been reported. Animal studies also suggest that combining this agent with calcineurin inhibitor could increase fetal toxicity, but studies in animals do not necessarily correlate with findings in human pregnancies³⁶.

E-Polyclonal antibodies (eg, antithymocyte globulins=ATG)

These agents are derived by injecting animals with human lymphoid cells, then harvesting and purifying the resultant antibody. ATG induces the complement lysis of lymphocytes and uptake of lymphocytes by the reticuloendothelial system and mask the lymphoid cell-surface receptors. These agents are used for induction and acute rejection. effects include fever. Adverse chills. thrombocytopenia, leukopenia. hemolysis, respiratory distress, serum sickness and anaphylaxis. Some adverse effects are ameliorated with steroids, acetaminophen, and diphenhydramine. There are no reported data on the teratogenic effect of ATG.

VI. CONCLUSION

In conclusion, successful pregnancies have been reported in female recipients of kidney, liver, pancreas-liver, heart, and lung transplants. Data collected in the NTPR provide the most extensive information on pregnancy outcomes both renal and non-renal solid organ recipient groups.



Immunosuppressive agents are required to graft rejection; no specific prevent combination is superior. Even as progress the medical and occurs in surgical management of pregnancy in recipients of transplants. solid-organ health care professionals and transplant recipients should consider the potential risks of pregnancy as well as the risks for the offspring. Pregnant transplant recipients are at increased risk of preeclampsia, preterm birth, and intrauterine growth restriction compared with the general pregnant population. Cautious prenatal care, using a multidisciplinary approach with communication among specialists, may help to ensure the safety of mother and infant.

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