Chapter 14
Transplant and Pregnancy

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Introduction

Greater than half of female kidney transplant recipients are of childbearing age, thus, preconception counseling, contraceptive management, and family planning are of great importance in the routine care of the female transplant recipient. Chronic kidney disease occurs for many reasons including hypertension, diabetes, autoimmune diseases, and various forms of glomerulonephritis. All ages can be affected, and some cases progress to end-stage renal disease (ESRD, or renal failure) early in life. Chronic kidney disease adversely affects female sexual function and fertility, with a reported fertility rate in women with ESRD on dialysis of less than 1% per year [1]. However, fertility rates improve significantly after kidney transplantation compared with during dialysis, often within months of transplantation. The first documented successful pregnancy with a live birth in a kidney transplant recipient in 1958 marked a new era in the quality of life improvements after transplantation.

Fertility in Transplant Recipients

End Stage Renal Disease leads to complex dysfunction of the Hypothalamic-Pituitary-Gonadal axis and resultant secondary amenorrhea [2, 3]. Renal replacement therapy does not restore fertility, and successful pregnancy with a live birth in a patient with ESRD is rarely reported. Furthermore, fetal outcomes in this setting are poor, with an estimated infant survival rate of 40–50% [1].

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Fertility rates are thought to significantly improve following kidney transplantation, although exact data are unclear, mainly relying on volunteer registries. One US-based study using Medicare claims data of more than 16,000 women in the first 3 years following kidney transplantation reveals pregnancy and live birth rates of 33 per 1000 and 19 per thousand female transplant recipients, significantly lower than the general American population over the time period studied [4].

In a study comparing 63 female kidney transplant recipients of childbearing age to 50 healthy women, there was no significant difference between groups in rates of regular menstruation or in the percentage of women with observed ovulatory cycles [3]. Menstrual regulation and ovulation rates are correlated with normalization of allograft function [2, 3, 5]. Circulating sex steroids are initially suppressed immediately following kidney transplantation but return to normal levels within 1 year [6].

Given the reliance on volunteer registry data and small case series, the rates of infertility or use of assistive reproductive technology following kidney transplantation are not clear [2]. mTOR inhibitors such as sirolimus do have an adverse effect on male fertility, although the impact on female reproductive function is unknown [7].

Pre-conception Counseling

Optimal timing of pregnancy is at least 1–2 years after transplantation [2, 8–12]. This recommendation is supported by data showing an increased risk of nonviable outcomes in the immediate post-transplant period (47% nonviable pregnancies less than 6 months after transplant, compared with 28% in the 6–24-month interval after transplant, and 19% after 24 months) [10]. A transplantation-to-conception interval greater than 5 years is associated with longer gestational ages and higher mean birth weights without an increased risk of pregnancy-related allograft loss [10].

The contraceptive choice is determined based on the general medical condition of the patient as well as the potential risks of additional sex hormone delivery. Women with uncomplicated solid organ transplants, in general, are classified as having an acceptable risk to benefit ratio for all forms of contraception. In contrast, in high-risk solid organ transplant recipients, oral contraceptives are ill-advised [13]. Combined oral contraceptives may impair hepatic metabolism of calcineurin inhibitors, corticosteroids, and sirolimus [14]. In addition, hypertensive patients and women over the age of 35 are advised to avoid oral contraceptives.

Long-acting reversible contraception with intrauterine devices may provide a more favorable option for transplant recipients, with minimal risks and high efficacy [14].

Recommended Criteria for Considering Pregnancy in Transplant Recipients

Maternal allograft survival and fetal outcomes are related to maternal renal function at the time of conception; thus, stable and adequate allograft function is a critical part of the prenatal assessment. Serum creatinine should optimally be less than 1.5 although some groups accept a creatinine of 2.0 or less, and there should be no recent history of allograft rejection. In addition, blood pressure should be less than 140/90 mmHg, proteinuria should be stable and less than 500 mg daily, comorbidities such as diabetes mellitus or systemic lupus erythematosus (SLE) should be medically optimized, and the patient should be on a stable immunosuppression regimen [8–11]. Rhesus (Rh) factor compatibility of patient and transplant, as well as cytomegalovirus (CMV), hepatitis B, herpes simplex virus (HSV), and toxoplasmosis status, should be established prior to conception [15]. Rubella vaccination should be done before transplantation but can be provided at the time of preconception counseling if necessary [10]. Potential teratogens including ACE-inhibitors, statins, mycophenolate mofetil, and mTOR inhibitors should be discontinued at least 6 weeks prior to planned conception [12]. Patients may transition to azathioprine and prednisone. Calcineurin inhibitor therapy may be essential to prevent allograft rejection in many patients, and the use of cyclosporine or tacrolimus is not a barrier to planned conception [2].

The pre-existing disease may influence maternal and fetal outcomes, and this should be considered in addition to the clinical parameters noted above [16]. Patients with SLE are at higher risk for complications in pregnancy, including preeclampsia, preterm labor, and maternal death, and risk is higher with active disease [17]. A minimum of 6 months of disease quiescence is therefore recommended prior to conception [18]. In addition, patients with lupus nephritis should be offered screening for Ro and La Antibody, which impart risk for fetal heart block and neonatal cutaneous lupus [16]. Patients with known genetic disorders such as Alport Syndrome and Polycystic Kidney Disease should be counseled regarding risk of inheritance. Case reports of onset of atypical HUS in pregnancy and the post-partum period, with a high incidence of complement abnormalities, raises concern that pregnancy carries a risk for disease reactivation in aHUS [19].

Pregnancy Outcomes in Transplant Recipients

Although most pregnancies following renal transplantation are successful, these are still classified as high-risk. Compared to control subjects, kidney recipients have a significantly higher risk of hypertension, preeclampsia, gestational diabetes, preterm delivery, intrauterine growth restriction (IUGR), low birth weight, and

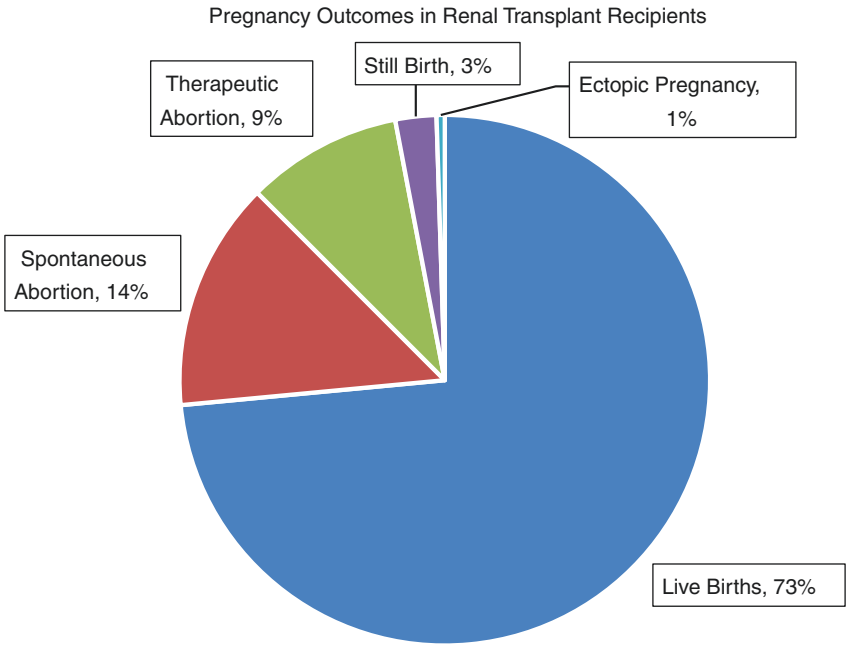

Fig. 14.1 Pregnancy outcomes in kidney transplant recipients. (Retrieved data from a meta-analysis of 50 studies worldwide published by Deshpande and colleagues, 2011 [21])

cesarean section [5, 16, 20–22]. Over 50% of pregnant transplant recipients are hypertensive, and the incidence of preeclampsia approaches 30% [21]. The incidence of preterm delivery is 47% with mean gestational age of 35.6 weeks [21]. Pregnancy outcomes are outlined in Fig. 14.1.

Effect of Pregnancy on Allograft Function

Pre-pregnancy allograft function is the most prominent factor influencing long-term post-pregnancy renal function. Although data are limited to case-control studies, most evidence suggests that antepartum graft function is unlikely to be adversely affected by pregnancy in women with serum creatinine less than 1.5 mg/dL who are treated with prednisone and azathioprine (AZA) [2, 15, 22].

The impact of pregnancy on long-term graft survival, particularly in women using calcineurin inhibitors, is unclear and remains an area of controversy. The increased glomerular filtration rate seen during pregnancy may damage allograft glomeruli, leading to progressive glomerular sclerosis [23]. Ten to fifteen percent of women with good allograft function before pregnancy will experience a decline in renal function during pregnancy that may be permanent [2]. Additionally, 11% of

transplant recipients develop new long-term medical problems postpartum, although it is unclear if pregnancy plays a causative role in this [24]. To date most case-control studies suggest that there is no significant difference in graft survival between pregnant and non-pregnant kidney transplant recipients [2, 10].

Medical and Obstetric Management of The Pregnant Kidney Transplant Patient

Given the multiple potential complications kidney transplant patients face, including rejection, infection, and immunosuppressant intolerance and dosing changes, a suggested management scheme is outlined in Table 14.1.

Table 14.1 Management scheme during pregnancy for the renal transplant recipient

Test/visit	When	Rationale
Before conception		
Rubella vaccine	Pre-transplantation	Live virus vaccine not recommended post-transplantation due to immune suppressants.
Rh compatibility of patient and allograft	Pre-pregnancy	If the patient is Rh negative but the kidney is Rh positive, there is a risk of maternal sensitization to Rh
Hepatitis B, C, HSV, CMV, HIV, toxoplasmosis, and rubella titers	Pre-pregnancy	Counsel regarding the risk of transmission. Hepatitis B vaccine can be given. Cervical cultures should be checked if HSV positive.
Stop mycophenolate, sirolimus, everolimus, and ACE-inhibitors 6 weeks prior to conception.	Pre-pregnancy	These agents are contraindicated in pregnancy due to the risk of fetal anomalies.
Stop statins 6 weeks prior to conception	Pre-pregnancy	Fetal risk of first-trimester statin use is not clear.
Urine culture	Pre-pregnancy	Risk of ascending asymptomatic bacteriuria and pyelonephritis
Consultation with a high-risk obstetrician	Pre-pregnancy	High-risk pregnancy with the likelihood of preterm delivery.
During pregnancy		
Blood pressure	Twice daily	High risk of hypertension in the transplant population.
Start low dose aspirin	Daily, beginning at 12 weeks gestation.	High risk of preeclampsia in the transplant population.
Allograft ultrasound	First trimester	Baseline to assess for hydronephrosis prior to significant uterine enlargement.

(continued)

Table 14.1 (continued)

Test/visit	When	Rationale
Clinic visits	Every 2–3 weeks up to 20 weeks; every 2 weeks until 28 weeks; every week after this	High-risk pregnancy with the likelihood of preterm delivery.
Fetal ultrasound	First trimester: Dating 20 weeks: Targeted scan for anomalies After 24–25 weeks: Every 3–4 weeks for growth	No increased risk of fetal anomalies with most immunosuppressive regimens (cyclosporine, tacrolimus, azathioprine, corticosteroids)
Antenatal testing: Nonstress test or BPP, Doppler if growth restricted	Weekly at 30–32 weeks	Increased risk of placental dysfunction
Liver function tests	Every 6 weeks (if on azathioprine)	Screen for azathioprine hepatotoxicity
CBC	Every 2–6 weeks	Decreased WBC may predict neutropenia in the newborn. If anemia present and iron deficiency excluded, erythropoiesis-stimulating agents (ESA) may be used.
Calcium and phosphorous	At start and PRN	May have tertiary hyperparathyroidism or history of subtotal parathyroidectomy
Glucose tolerance test	Each trimester Depending on which immunosuppressants Are used.	Many patients are on steroids and tacrolimus, and insulin resistance is common.
Serum BUN, creatinine, calculated clearance, and proteinuria.	Every 2–4 weeks	Screening for rejection and preeclampsia
Calcineurin inhibitor levels	Every 1–2 weeks	The volume of distribution changes with increased maternal blood volumes
IgM to toxoplasmosis	Each trimester if seronegative	Risk of congenital infection
IgM to CMV	Each trimester if seronegative	Risk of congenital infection
Examine for HSV lesions	At labor	May affect the approach to delivery
Urine dipstick	Each visit, with cultures every month	Risk of ascending asymptomatic bacteriuria and pyelonephritis
Kidney biopsy	Unexplained decrease in allograft function	Rarely done during pregnancy
Postpartum		
Blood pressure	Twice daily for 6 weeks	Screening for gestational hypertension
Serum BUN, creatinine, calculated clearance, and proteinuria.	1 month and 6 months postpartum	Screening for rejection and preeclampsia

Adapted from Josephson and McKay, 2007 and Hou, 2013, the European Best Practice Guidelines for Transplantation, 2002, and the US Preventative Services Task Force [2, 9, 25, 26]

Immunosuppressant Selection and Monitoring

Selection of immunosuppressant agents in pregnant patients requires balancing the risks of allograft rejection with fetal injury or loss. Most immunosuppressive agents cross the placenta, resulting in fetal exposure and possible risk. In practice, there is extensive experience with most agents in pregnancy. Standard immunosuppression generally consists of two to three agents: a calcineurin inhibitor that primarily inhibits T cell activation, an anti-proliferative agent that hinders T and B cell division, and/or corticosteroids that prevent a variety of lymphocyte activation steps. There is a "privileged immunologic status" of pregnancy that allows for maternal tolerance of her "fetal allograft" [27]. Pregnant women are not, however, systemically immunosuppressed. This mechanism, which prevents fetal rejection, is not active in the renal allograft and, therefore, does not translate into a lower requirement for systemic immunosuppression or risk of rejection during pregnancy.

Corticosteroids

If already being taken, corticosteroids should be continued during pregnancy. Both prednisone and prednisolone cross the placenta, but placental metabolism converts them to less active forms. There are case reports of fetal adrenal insufficiency and thymic hypoplasia with high-dose corticosteroid treatment, but this is rare when the total daily dose is kept at 15 mg or less [15, 25]. In the setting of acute rejection, however, high-dose steroids should be used [9].

Calcineurin Inhibitors

Calcineurin inhibitors (cyclosporine (CSA) and tacrolimus) prevent T cell activation and should be continued during pregnancy. CSA crosses the placenta with fetal exposure similar to maternal drug levels, and tacrolimus crosses less readily, with cord blood tacrolimus levels less than 50% of maternal serum levels [28, 29]. Cyclosporine has not been associated with congenital malformations but carries a small risk of fetal growth restriction [15, 25, 30]. Tacrolimus is associated with less hypertension and hyperlipidemia compared to CSA [20, 30]. Cyclosporine and tacrolimus levels usually decrease during pregnancy due to the increased volume of distribution, although hepatic metabolism may slow due to high levels of sex steroids [2, 25]. Higher doses may be needed to prevent allograft rejection during pregnancy [31]. Current recommendations are to adjust dosing to maintain pre-pregnancy therapeutic levels [9, 18].

Inhibitors of Purine Synthesis

All antiproliferative agents are classified by the FDA as category D, but azathioprine (AZA) is the safest and most widely used in pregnant transplant patients. Azathioprine is a pro-drug whose active form inhibits purine metabolism. The fetal liver lacks the enzyme necessary for conversion of AZA to the active metabolite [15, 25]. Azathioprine is reported to cause rodent fetal abnormalities and rare case reports of birth defects in human fetuses [25]. There has been no evidence of fetal anomalies with dosing less than 2 mg/kg/day [9]. AZA also has been associated with dose-related fetal myelosuppression (suppression of blood-forming elements), but clinically relevant leukopenia is rare.

Mycophenolate mofetil (MMF) is a purine synthesis inhibitor that largely has replaced AZA in non-pregnant patients. Because MMF used during pregnancy is associated with a higher incidence of fetal structural malformations compared to other agents, the FDA and international guidelines have contraindicated MMF in pregnancy [20, 32, 33]. MMF should be stopped 6 weeks prior to conception and substituted with AZA [2, 9].

mTOR Inhibitors

Sirolimus is a newer anti-proliferative agent that also is contraindicated in pregnancy because fetal toxicity is reported in animals. Due to serious concerns regarding fetal risk, there are limited human data. Existing registry data and case reports regarding the use of sirolimus or everolimus during early pregnancy do not reveal a clear risk of congenital abnormalities [2]. Sirolimus generally is substituted with CSA or tacrolimus during pregnancy.

Biologic Agents

Belatacept is a novel soluble fusion protein that blocks the co-stimulation of T cells. This protein is closely related to Abatacept, which has been studied more extensively in patients with rheumatoid arthritis. To date, there are no studies evaluating the safety of belatacept in pregnancy, although the National Transplant Pregnancy Registry in the US is extending efforts to collect data on belatacept use [2]. Animal studies have not revealed a risk of congenital abnormalities with abatacept or belatacept exposure, although there is a possible risk of autoimmunity in murine offspring. Studies of abatacept in pregnancy have revealed no pattern of congenital abnormalities associated with either maternal or paternal drug exposure [34]. Use of these agents in pregnancy should only be considered in cases where the potential maternal benefit justifies the potential fetal risk.

Rituximab is a monoclonal antibody directed against CD-20 positive B cells. Immunoglobulin G crosses the placenta, with increasing efficiency as pregnancy progresses. Although there is limited information regarding the safety of rituximab in pregnancy, given concerns regarding infection risk (particularly maternal susceptibility to CMV), conception should be delayed for at least 1 year following Rituximab exposure [2, 35].

Common Complications

Hypertension

Hypertension is seen in one of every two to five pregnant transplant recipients [21, 25]. Hypertension during pregnancy increases the risk of preterm delivery, growth restriction, and *abruptio placentae*. Target blood pressure levels for pregnant renal transplant recipients are the same as for non-pregnant patients with renal insufficiency; the goal is less than 140/90 mmHg [36]. All kidney transplant recipients should monitor their blood pressures daily during pregnancy, (Table 14.1) [2, 9, 25]. The preferred agent for treatment of hypertension during pregnancy is alpha methyldopa; however, labetalol, calcium channel blockers, alpha blockers, thiazide diuretics, clonidine, and hydralazine, all are considered safe during pregnancy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are absolutely contraindicated given their association with fetal congenital defects. They should be discontinued prior to conception or promptly upon confirming pregnancy. In transplant recipients with volume expansion, diuretics may be required for adequate blood pressure control [9, 23, 27].

Preeclampsia

The incidence of preeclampsia is approximately 27% in kidney transplant recipients [16, 21], which is significantly higher than the general population. The diagnosis of preeclampsia, however, is challenging given the common occurrence of pre-existent hypertension and proteinuria in kidney transplant recipients. Calcineurin inhibitors also raise uric acid levels, making the uric acid level a less useful serum marker for preeclampsia. Therefore, there should be a low threshold to hospitalize for hypertension in pregnant kidney transplant recipients [15]. Current guidelines support the use of low dose aspirin starting at 12 weeks gestation in patients at high risk for preeclampsia [2, 26]. Pregnant transplant recipients with preeclampsia should be delivered expeditiously. Progression to eclampsia in a transplant recipient, as in any other pregnancy, is an obstetric emergency.

Bacterial Infections

Pregnant kidney transplant recipients are at higher risk for bacterial infections, particularly of the urinary tract due to the pregnancy-related alterations in physiology. The incidence of urinary tract infection in pregnant kidney transplant recipients may be as high as 40%, and uncommon organisms must be considered [37]. The current recommendation is monthly screening urine cultures [2, 9, 25, 37]. If asymptomatic bacteriuria is diagnosed, these patients should receive two weeks of antimicrobial therapy; they may require suppressive antibiotics if this recurs.

Progressive Kidney Injury

Pregnant transplant recipients are at risk for renal insufficiency from pyelonephritis, preeclampsia, calcineurin inhibitor toxicity, obstruction, acute or chronic rejection, and recurrent disease. Some of these etiologies may present similarly, posing a diagnostic challenge to the clinician. It is most important to distinguish between preeclampsia and acute rejection as causes of acute kidney injury in the pregnant patient because the former is treated with delivery and the latter with high-dose steroids. Unfortunately, progressive proteinuria, increased uric acid levels, and hypertension can occur in the setting of renal insufficiency of any cause and it, therefore, can be difficult to distinguish between preeclampsia and acute rejection. An ultrasound-guided kidney biopsy may be necessary in these settings, particularly when delivery poses a significant risk to the fetus.

Ureteral obstruction of the transplanted kidney by the gravid uterus is uncommon, but it has been reported [15]. Furthermore, interpretation of hydronephrosis in the transplanted kidney is difficult, because there often is mild baseline hydronephrosis following transplant or during pregnancy. A baseline allograft ultrasound in the first trimester is recommended for this reason.

The incidence of reported acute rejections during pregnancy or within 3 months postpartum is about 10–15%, which is similar to the reported rate in non-pregnant women [2, 9, 25]. There is concern that rejections are under-diagnosed because of the expected drop in serum creatinine that occurs during pregnancy [25], and transplant recipients are at risk for acute rejection in the postpartum period. Acute rejection should be confirmed by allograft biopsy and is treated with high-dose steroids [11]. Data regarding anti-thymocyte globulin (ATG) use is limited to case reports, with limited evidence of successful and safe outcomes in pregnancy [18].

Labor and Delivery

The anatomic location of the renal allograft in the postero-lateral pelvis does not interfere with normal vaginal delivery, and a decision to perform cesarean section is based on usual obstetric indications [25]. It is advisable for pregnant transplant

recipients to have a formal consultation with a transplant surgeon with a surgical plan for cesarean section should it become necessary. If felt indicated, a transplant surgeon can be present in the operating room if a cesarean section is to be done, although a transplanted kidney normally is not in the obstetrician's operative field. There may be an increased risk of ureteral injury with a low-transverse incision, but this is rare.

Breastfeeding

Breastfeeding in the setting of immunosuppression has been controversial, and prior guidelines recommended against breastfeeding, citing the risk of drug exposure. More recent literature notes that, in women taking prednisone, azathioprine, and cyclosporine or tacrolimus, there have been no evident adverse effects on their breastfed infants [12, 38]. In addition, fetal exposure to these same medications exceeds the potential exposure in breastmilk [38]. Considering the many potential benefits of breastmilk in neonates, particularly those at risk for low birth weight and premature delivery, there is a trend towards acceptance of breastfeeding as an option for mothers using the above immunosuppressive agents. As of 2012, 36% of women participating in the National Pregnancy Transplant registry, a US-based volunteer registry, reported breastfeeding, increased from <5% in 1995 [38].

In contrast, alternative agents including MMF, sirolimus, or belatacept, do not carry sufficient clinical safety data, and breastfeeding should be avoided when using these medications.

Summary

In summary, the return of fertility is a benefit of kidney transplantation in women of childbearing age. Pregnancy in a kidney transplant recipient is considered high risk and requires a multidisciplinary approach with frequent monitoring. However, with careful assessment of maternal renal function, immunosuppression, infection surveillance, and fetal growth, the likelihood of a favorable perinatal outcome can be optimized.

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