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PREGNANCY AFTER KIDNEY TRANSPLANTATION: CURRENT APPROACHES TO ALLOGRAFT MONITORING AND MATERNAL OUTCOMES

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ABSTRACT

Pregnancy after kidney transplantation is increasingly achievable, but it remains a high-risk condition requiring coordinated nephrological, transplant, and obstetric care. This review summarizes current evidence on maternal outcomes and approaches to kidney allograft monitoring before conception, during pregnancy, and in the postpartum period. Available meta-analyses show high live-birth rates among kidney transplant recipients, while preeclampsia, hypertensive disorders, preterm birth, infection, and acute allograft rejection remain important complications. Favorable outcomes are most strongly associated with stable baseline allograft function, minimal proteinuria, controlled blood pressure, absence of recent rejection, and pregnancy-compatible immunosuppression. Monitoring should include serial assessment of serum creatinine, proteinuria, blood pressure, urinary infection, and calcineurin-inhibitor concentrations, with particular attention to pregnancy-related pharmacokinetic changes in tacrolimus. Because conventional eGFR equations are not well validated in pregnancy, creatinine trends should be interpreted against individual baseline values and the overall clinical context. Deterioration in allograft function requires careful differentiation among preeclampsia, infection, obstruction, drug toxicity, volume depletion, and acute rejection. Postpartum surveillance is also essential because hemodynamic and pharmacokinetic changes may alter allograft function and immunosuppressive exposure. Current evidence suggests that pregnancy does not necessarily worsen long-term allograft survival in appropriately selected women, although standardized monitoring strategies and better validated biomarkers of early allograft injury are still needed.

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Keywords: *kidney transplantation; pregnancy; kidney allograft function; preeclampsia; immunosuppression; tacrolimus.*

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Introduction

Kidney transplantation is the most effective form of renal replacement therapy for patients with end-stage kidney disease and is associated with substantial improvements in overall health, quality of life, and reproductive function. Restoration of kidney function following transplantation generally leads to normalization of the hypothalamic–pituitary–gonadal axis and recovery of fertility, making pregnancy feasible for a considerable proportion of women of reproductive age. However, pregnancy in kidney

transplant recipients remains a high-risk condition and requires multidisciplinary care involving transplant physicians, nephrologists, and obstetricians. Over the past several decades, accumulating evidence has demonstrated that pregnancy after kidney transplantation can result in a live birth in the majority of cases, although the incidence of complications remains higher than in the general population. A systematic review and meta-analysis including 50 studies, 4,706 pregnancies, and 3,570 kidney transplant recipients reported a live-birth rate of 73.5%, a preeclampsia rate of 27.0%, gestational diabetes mellitus in 8.0% of pregnancies, cesarean delivery in 56.9%, and preterm birth in 45.6%. The authors emphasized that more favorable outcomes were observed among patients with a lower-risk profile and better baseline allograft function (Deshpande et al., 2011).

More recent evidence confirms the persistently high incidence of obstetric complications in this population. A 2024 meta-analysis including 109 studies, 7,708 pregnancies, and 5,107 kidney transplant recipients reported a live-birth rate of 78.48%, preeclampsia in 20.87%, hypertensive disorders of pregnancy in 24.30%, preterm birth in 45.30%, and acute allograft rejection in 8.06% of cases. Allograft loss following pregnancy was reported in 123 of 853 patients for whom relevant outcome data were available (Mustafa et al., 2024).

Thus, although the number of successful pregnancies after kidney transplantation has increased, substantial maternal, obstetric, and nephrological risks remain. Interpretation of complication rates requires consideration of baseline allograft function, the presence of proteinuria and arterial hypertension, the time elapsed since transplantation, and the type of immunosuppressive therapy.

One of the most important determinants of pregnancy outcomes is the functional status of the kidney allograft before conception. The most favorable clinical profile is generally characterized by stable allograft function, absent or minimal proteinuria, well-controlled blood pressure, and no recent episodes of acute rejection.

According to a position statement from the Italian Society of Nephrology, a relatively favorable preconception profile includes an estimated glomerular filtration rate (eGFR) of ≥60 mL/min, absent or minimal proteinuria, well-controlled blood pressure, no recent rejection episodes, stable immunosuppressive therapy, and the absence of potentially teratogenic medications. Reduced allograft function, proteinuria, and hypertension are associated with an increased risk of deterioration in kidney function and adverse pregnancy outcomes (Cabiddu et al., 2018).

Proteinuria deserves particular attention because it may represent either a manifestation of pre-existing chronic allograft injury or an early marker of preeclampsia. Therefore, assessment of 24-hour urinary protein excretion or the urinary protein-to-creatinine ratio before conception and throughout pregnancy is essential for differentiating obstetric complications from transplant-related pathology.

Physiological pregnancy is accompanied by increases in circulating blood volume and renal blood flow, as well as an increase in glomerular filtration. In kidney transplant recipients, these physiological changes occur in the setting of a limited functional reserve of the transplanted kidney.

Some patients experience increases in serum creatinine, urea, and proteinuria during pregnancy. However, transient changes in allograft function do not necessarily indicate acute rejection. In a study evaluating kidney allograft function during pregnancy, allograft dysfunction was observed in a proportion of patients and was primarily associated with preeclampsia and, less frequently, with rejection, urinary tract obstruction, or infection. In most patients, these changes were transient (Aivazoglou et al., 2011).

This finding has important clinical implications because an increase in serum creatinine during pregnancy requires careful assessment of its underlying cause. The differential diagnosis should include preeclampsia, urinary tract infection and graft pyelonephritis, obstructive complications, calcineurin inhibitor nephrotoxicity, volume depletion, and acute allograft rejection.

Recent evidence also highlights the importance of specifically evaluating allograft function during the postpartum period. A systematic review and meta-analysis of 38 studies reported an approximately

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9.4% risk of allograft loss within the first two years following pregnancy, although allograft function generally remained stable thereafter in patients with a functioning graft. Baseline proteinuria, arterial hypertension, and higher serum creatinine levels before pregnancy were identified as important risk factors for adverse outcomes (van Buren et al., 2020).

A more recent 2025 meta-analysis comparing pregnant and non-pregnant kidney transplant recipients likewise found no statistically significant increase in the risk of allograft loss among women who had experienced pregnancy compared with controls. Nevertheless, a modest increase in serum creatinine was observed after delivery, emphasizing the need for continued and structured postpartum monitoring (Kanbay et al., 2025).

Arterial hypertension is one of the most common complications of pregnancy in kidney transplant recipients. Pre-existing hypertension, particularly when accompanied by proteinuria and impaired allograft function, is associated with an increased risk of preeclampsia and deterioration of kidney function. According to a recent meta-analysis, hypertensive disorders of pregnancy occur in approximately one-quarter of kidney transplant recipients, while preeclampsia affects approximately one in five patients (Mustafa et al., 2024).

The diagnosis of preeclampsia in kidney transplant recipients can be challenging. Chronic hypertension, pre-existing proteinuria, and abnormalities in kidney function may be present before conception and can mimic manifestations of preeclampsia. Therefore, diagnosis should not rely on a single laboratory parameter but should be based on the dynamics of clinical and laboratory findings and their overall clinical context.

Maintaining adequate immunosuppression is essential for preserving kidney allograft function during pregnancy. At the same time, potential fetal exposure to medications with teratogenic effects must be minimized. Immunosuppressive agents that are generally considered compatible with pregnancy after kidney transplantation include tacrolimus, cyclosporine, azathioprine, and corticosteroids. In contrast, mycophenolic acid preparations and mammalian target of rapamycin (mTOR) inhibitors should not be used during pregnancy planning and require substitution before conception. KDIGO recommends discontinuation or replacement of mycophenolate before attempts at conception and recommends replacement of mTOR inhibitors. Particular attention has been devoted to tacrolimus. Pregnancy is associated with substantial pharmacokinetic changes that may result in a decrease in whole-blood tacrolimus concentrations despite preservation or even an increase in the unbound fraction of the drug. These changes are partly related to reduced serum albumin concentrations and alterations in hematological parameters. Consequently, interpretation of tacrolimus exposure based solely on whole-blood trough concentrations may be challenging (Hebert et al., 2013).

Clinical studies have shown that maintaining therapeutic tacrolimus concentrations during pregnancy often requires an increase in the daily dose. In one observational series, the mean tacrolimus dose increased from 3.2 mg/day to 7.3 mg/day during the third trimester and subsequently decreased after delivery (Aktürk et al., 2015).

Therefore, a decline in tacrolimus blood concentration during pregnancy should not automatically be interpreted as poor adherence to treatment. It may reflect physiological pharmacokinetic changes associated with pregnancy. Regular therapeutic drug monitoring, together with serial assessment of allograft function, is therefore essential.

Pregnancy in the setting of immunosuppressive therapy is associated with an increased clinical significance of infectious complications. Urinary tract infections and graft pyelonephritis are of particular concern.

European recommendations for the management of kidney transplant recipients have emphasized the importance of regular urinalysis and urine cultures during pregnancy because urinary tract infections

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may be asymptomatic and may pose a risk to both maternal health and allograft function (EBPG Expert Group on Renal Transplantation, 2002).

Infectious inflammation of the transplanted kidney may result in increased serum creatinine and proteinuria and can therefore mimic acute allograft rejection. Consequently, when allograft function deteriorates during pregnancy, infectious, immunological, and obstetric causes should be evaluated concurrently.

Despite concerns regarding immunological changes during pregnancy, acute allograft rejection is relatively uncommon in patients with stable baseline allograft function and adequate immunosuppression. Nevertheless, its clinical significance remains substantial because rejection may result in irreversible allograft injury and loss.

In the 2024 meta-analysis, acute rejection was reported in approximately 8% of pregnancies, although the incidence varied considerably across individual studies (Mustafa et al., 2024).

The postpartum period should also be taken into consideration. Historical studies have documented episodes of acute rejection after delivery, supporting the need for continued close monitoring of allograft function and immunosuppressive drug concentrations during the postpartum period (Marushak et al., 1986).

Current approaches consider pregnancy after kidney transplantation a multidisciplinary process that should begin before conception and continue throughout pregnancy and the postpartum period. Preconception assessment should include evaluation of kidney allograft function, serum creatinine, proteinuria, blood pressure, potential infectious foci, stability of immunosuppressive therapy, and the absence of recent rejection episodes.

During pregnancy, regular monitoring should include complete blood count, urinalysis, proteinuria, serum creatinine, urea, electrolytes, liver function tests, blood pressure, and concentrations of calcineurin inhibitors. An Italian expert group recommends nephrological follow-up with laboratory assessment at least every 2–4 weeks in patients with good allograft function and without proteinuria or hypertension, with more frequent monitoring in patients with additional risk factors (Cabiddu et al., 2018).

Assessment of estimated glomerular filtration rate represents a particular challenge. Equations developed for non-pregnant populations have not been adequately validated for reliable estimation of GFR during pregnancy in kidney transplant recipients. Therefore, changes in serum creatinine should be interpreted in relation to the patient's baseline values and the overall clinical context. The postpartum period represents an important stage of follow-up because the cessation of pregnancy-related physiological changes is accompanied by alterations in the pharmacokinetics of immunosuppressive drugs, hemodynamics, and fluid and electrolyte balance.

Following delivery, monitoring of serum creatinine, proteinuria, blood pressure, and tacrolimus or cyclosporine concentrations should be continued. Particular attention should be paid to changes in tacrolimus exposure because doses increased during pregnancy may become excessive after delivery. Pharmacokinetic studies have demonstrated substantial changes in tacrolimus disposition during pregnancy, followed by restoration of the pre-pregnancy pharmacokinetic profile after delivery (Versluis et al., 2024).

Overall, current evidence suggests that pregnancy itself does not necessarily compromise long-term allograft survival in women with stable kidney allograft function. A systematic review and meta-analysis of long-term outcomes found no significant difference in allograft survival between women who became pregnant and matched non-pregnant kidney transplant recipients.

Despite the substantial increase in published evidence, most studies of pregnancy after kidney transplantation remain retrospective, single-center, or registry-based. The relatively small number of patients in individual studies limits the ability to establish precise threshold values for serum creatinine, proteinuria, and eGFR that reliably define pregnancy-related risk (van Buren et al., 2020).

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In addition, early biomarkers of allograft injury that could identify dysfunction before a clinically significant increase in serum creatinine remain insufficiently studied. In this context, emerging biomarkers of renal injury, including neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and urinary microalbumin, represent potentially valuable tools, particularly in pregnant kidney transplant recipients in whom conventional assessment of allograft function is complicated by the physiological changes of pregnancy.

Conclusion. Current evidence indicates that pregnancy after kidney transplantation is feasible and can result in favorable outcomes in most appropriately selected patients receiving careful multidisciplinary monitoring. The principal factors associated with adverse outcomes include baseline allograft function, proteinuria, arterial hypertension, previous episodes of rejection, infection, and the characteristics of immunosuppressive therapy. The most frequently reported complications include preeclampsia, hypertensive disorders of pregnancy, urinary tract infections, anemia, preterm birth, and fetal growth restriction.

A major challenge in transplant medicine is the timely differentiation of physiological changes associated with pregnancy from obstetric complications and true kidney allograft dysfunction. Regular assessment of serum creatinine, proteinuria, blood pressure, infectious markers, and immunosuppressive drug concentrations, complemented by emerging biomarkers of allograft injury, may improve the early detection of clinically significant complications.

Therefore, the development of a standardized monitoring algorithm for kidney transplant recipients during pregnancy and the postpartum period remains an important clinical and research priority.

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