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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Is pregnancy safe after kidney transplant?

Breast-feeding is considered safe for renal transplant recipients taking prednisone, azathioprine, cyclosporine, and tacrolimus

A: Since the first successful pregnancy in a kidney transplant recipient in 1958,[1] hundreds of kidney recipients have had successful pregnancies. Chronic kidney disease disrupts the hypothalamic-pituitary-gonadal axis, leading to anovulation and infertility. However, within 6 months of kidney transplant, the hypothalamic-pituitary-gonadal axis and sex hormone levels return to normal,[2] and the renal allograft is able to adapt to the various physiologic changes of pregnancy.[3]

Successful pregnancy after kidney transplant requires a team approach to care that includes the primary care physician, a transplant nephrologist, and an obstetrician with expertise in high-risk pregnancies. But equally important is educating and counseling the patient about the risks and challenges. This should begin at the first pretransplant visit.[4]

Below are answers to questions often asked by renal transplant recipients who wish to become pregnant.

WHAT IS THE IDEAL TIME TO BECOME PREGNANT AFTER KIDNEY TRANSPLANT?

According to American Society of Transplantation and European best-practice guidelines, as outlined in **Table 1**, the ideal time to conceive is 1 to 2 years after renal transplant if graft function is stable, proteinuria is minimal, there are no recent episodes of acute rejection, and the patient is not taking teratogenic medications. Because transplant recipients take teratogenic immunosuppressive drugs such as mycophenolate mofetil, women should be counseled to start contraception as soon as possible after kidney transplant.[5,6]

Mycophenolate mofetil and sirolimus are contraindicated in pregnancy and should be stopped at least 6 weeks before conception. Mycophenolate mofetil increases the risk of congenital malformations and spontaneous abortion. Data on sirolimus from clinical studies are limited, but in animal studies it is associated with delay in ossification of skeletal structure and with an increase in fetal mortality.[7]

WHAT INCREASES THE RISK OF A POOR PREGNANCY OUTCOME AFTER RENAL TRANSPLANT?

Risk factors for poor maternal and fetal outcomes include an elevated prepregnancy serum creatinine level (≥ 1.4 mg/dL), hypertension, and proteinuria (≥ 500 mg/24 hours). Younger age at transplant and at conception is associated with better pregnancy outcome.[5,8]

WHAT ARE THE POSSIBLE MATERNAL COMPLICATIONS?

Kidney transplant recipients who become pregnant have a risk of developing preeclampsia 6 times higher than normal, and the incidence rate ranges between 24% and 38%.[9,10] The risk of cesarean delivery is 5 times higher than in the general population, and the incidence rate is 43% to 64%.[10,11]

Low-dose aspirin reduces the risk of preeclampsia and should be prescribed to all pregnant women who are kidney transplant recipients. Angiotensin-converting enzyme inhibitors are contraindicated due to the risk of teratogenic effects, ie, pulmonary hypoplasia and oligohydramnios.[4]

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WHAT ARE THE POSSIBLE FETAL COMPLICATIONS?

Women who become pregnant after kidney transplant are at greater risk of preterm delivery (40% to 60% higher risk), having a baby with low birth weight (42% to 46% higher risk), and intrauterine growth restriction (30% to 50% higher risk). But the risk of perinatal mortality is not increased in the absence of the above-mentioned risk factors.[10,11]

DOES PREGNANCY INCREASE THE RISK OF GRAFT FAILURE?

Pregnancy does not increase the risk of allograft loss as long as the patient has a prepregnancy serum creatinine below 1.4 mg/dL, no hypertension, and urine protein excretion less than 500 mg/24 hours.[12]

WHAT CHANGES TO IMMUNE SUPPRESSION ARE REQUIRED BEFORE AND DURING PREGNANCY?

Careful management of immunosuppression is critical in renal transplant recipients before and during pregnancy because of the risks of teratogenicity and other adverse effects.

As stated above, mycophenolate mofetil and sirolimus are teratogenic and should be stopped 6 weeks before conception. The recommended maintenance immunosuppression during pregnancy includes calcineurin inhibitors (tacrolimus and cyclosporine), azathioprine, and low-dose prednisone.

A 20% to 25% increase in the dose of calcineurin inhibitor is required during pregnancy due to an increase in metabolic activity of cytochrome P450 and an increase in the volume of distribution.[5,6,13] However, this dosing increase requires more frequent monitoring throughout the pregnancy to ensure the safest possible therapeutic levels.

TABLE 1

Criteria for pregnancy after renal transplant

From 1 to 2 years after transplant
Stable allograft function, creatinine < 1.4 mg/dL
No recent episodes of acute rejection
Blood pressure controlled to ≤ 140/90 mm Hg
No proteinuria, or proteinuria ≤ 500 mg/24 hours
Prednisone dosage ≤ 15 mg/day
Azathioprine dosage ≤ 2 mg/kg/day
Discontinue mycophenolate mofetil and sirolimus 6 weeks before conception

DOES PREGNANCY INCREASE THE RISK OF INFECTION?

Because of their immunosuppressed state, renal transplant recipients are prone to infection; the incidence rate of urinary tract infection is as high as 40% due to mild reflux and pregnancy-related dilation of ureters and collecting ducts.[6] Women should be screened for urinary tract infection at every visit with urine dipstick testing and with urine culture every 4 weeks. Antibiotics such as nitrofurantoin, amoxicillin, and cephalexin are safe to treat urinary tract infection during pregnancy.[6]

IS BREAST-FEEDING SAFE IN RENAL TRANSPLANT RECIPIENTS?

Breast-feeding is considered safe for women with renal transplant who are on prednisone, azathioprine, cyclosporine, and tacrolimus. Women should avoid breast-feeding if they are taking mycophenolate mofetil, sirolimus, everolimus, or belatacept, as clinical data on safety are not adequate.[14]

REFERENCES

1. **Murray JE, Reid DE, Harrison JH, Merrill JP**. Successful pregnancies after human renal transplantation. N Engl J Med 1963; 269:341–343.
2. **Saha MT, Saha HH, Niskanen LK, Salmela KT, Pasternack AI**. Time course of serum prolactin and sex hormones following successful renal transplantation. Nephron 2002; 92:735–737.
3. **Davison JM**. The effect of pregnancy on kidney function in renal allograft recipients. Kidney Int 1985; 27:74–79.
4. **Shah S, Verma P**. Overview of pregnancy in renal transplant patients. Int J Nephrol 2016; 2016:4539342.
5. **McKay DB, Josephson MA, Armenti VT, et al; Women's Health Committee of the American Society of Transplantation**. Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. Am J Transplant 2005; 5:1592–1599.
6. **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):50–55.
7. **Armenti VT, Moitz MJ, Cardonick EH, Davison JM**. Immunosuppression in pregnancy: choices for infant and maternal health. Drugs 2002; 62:2361–2375.

8. **Bramham K, Chusney G, Lee J, Lightstone L, Nelson-Piercy C**. Breastfeeding and tacrolimus: serial monitoring in breast-fed and bottle-fed infants. Clin J Am Soc Nephrol 2013; 8:563–567.
9. **Deshpande NA, James NT, Kucirka LM, et al**. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. Am J Transplant 2011; 11:2388–2404.
10. **Bramham K, Nelson-Piercy C, Gao H, et al**. Pregnancy in renal transplant recipients: a UK national cohort study. Clin J Am Soc Nephrol 2013; 8:290–298.
11. **Coscia LA, Constantinescu S, Moritz MJ, et al**. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2010: 65–85.
12. **Sibanda N, Briggs JD, Davison JM, Johnson RJ, Rudge CJ**. Pregnancy after organ transplantation: a report from the UK transplant pregnancy registry. Transplantation 2007; 83:1301–1307.
13. **Kim H, Jeong JC, Yang J, et al**. The optimal therapy of calcineurin inhibitors for pregnancy in kidney transplantation. Clin Transplant 2015; 29:142–148.
14. **Constantinescu S, Pai A, Coscia LA, Davison JM, Moritz MJ, Armenti VT**. Breast-feeding after transplantation. Best Pract Res Clin Obstet Gynaecol 2014; 28:1163–1173.

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