Pregnancy in Renal Transplant Recipients and Donors

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Summary: Women with renal transplants have restoration of fertility with improved kidney function; however, pregnancy rates in renal transplant recipients appear to be lower than the general population, which might be influenced by patient choice. Women with renal transplants need to evaluate potential neonatal outcomes, graft outcomes, and risks to their own health to make informed decisions about conception. Pregnancy should be carefully planned in renal transplant recipients to reduce risk for graft loss, optimize pregnancy outcomes, and ensure immunosuppression regimes are nonteratogenic. Neonatal outcomes remain significantly worse for women with renal transplants than healthy controls, particularly for those with reduced graft function, hence prepregnancy, antenatal, and postpartum care of women with renal transplants should be guided by a multidisciplinary team of nephrologists and specialist obstetricians.
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Women with severe chronic kidney disease are frequently recommended to delay conception until after transplantation to enable restoration of fertility and improve pregnancy outcomes. However, further complexity to pregnancy planning is introduced after renal transplantation, including optimal timing of conception, teratogenicity of immunosuppression, risk of graft loss, and concerns regarding mode of delivery. In addition, both maternal and neonatal pregnancy complications remain higher than they are for the general population, despite near normal glomerular filtration rates in many women with kidney transplants.

PREGNANCY RATES AND FERTILITY IN RENAL TRANSPLANT RECIPIENTS

The incidence of pregnancy was reported, in an assessment of Medicare data, to be considerably lower in women with renal transplants compared with the general population. A significant reduction in the pregnancy rate was seen between 1990 and 2000, which decreased from 59 to 20 pregnancies/1,000 transplant recipients.[1] Similarly, a lower rate of pregnancy compared with the Australian general population (0.19 [95% confidence interval 0.17 to 0.21]) was reported by the Australian and New Zealand Dialysis and Transplant Registry with a further decline during the same time period, particularly for women in their twenties.[2] Estimates of the proportion of women with renal transplants who become pregnant range from 2% to 5%,[3,4] despite over half of patients with renal transplants being of child-bearing age. The low pregnancy rate in women with renal transplants is unexplained, but it is possible that women choose not to conceive to preserve graft function. The decline in pregnancy rate with time might also be related to the introduction of mycophenolate mofetil in 1995, which is teratogenic, or it might be a consequence of improved prepregnancy counseling, but further qualitative analysis of decision-making regarding pregnancy in this population is needed.

There is limited understanding of fertility in women with renal transplants, but one Iranian study described infertility problems in 13 out of 126 (10.4%) women with renal transplants,[5] which is comparable with general population rates. A small prospective study reported that prolactin, luteinising hormone, and follicle stimulations hormone in seven women returned to normal within 14-21 days of restoration of renal function,[6] and numerous case reports describe ovulation[7] and even pregnancy within weeks after transplantation.[8] Nonetheless, the global trend to delay pregnancy is likely to contribute to lower pregnancy rates in women with renal transplants due to reduced fertility compounded by long waiting lists, which indirectly contribute to increased maternal age in this group.

TRANSPLANTATION-TO-CONCEPTION INTERVAL

Evidence for optimal timing for conception is limited to single center and retrospective studies, of which some report adverse pregnancy outcomes to be inversely related to the interval between transplantation and conception,[3,9–11] while others report no influence.[12–14] However, a meta-analysis of outcomes of 4,706 pregnancies in renal transplant recipients was suggestive that live-birth rates are higher in studies with a mean interval between transplantation and pregnancy of <2 years (80.1%) compared with studies with an interval

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of 2-3 years (64.2%), 3-4 years (76.1%), and >4 years (75.4%).[15] However, it is important to recognize that individual patients' data were not analyzed in this study, and only three studies had a mean interval of <2 years compared with 14 studies that had longer time intervals.[15] Furthermore, comparisons of intervals between transplantation and conception were made for other pregnancy outcomes, and the rates of preeclampsia, gestational diabetes, cesarean section, and preterm birth were more common in studies with a mean interval of <2 years between transplantation and conception than in studies with longer intervals.[15]

A recent retrospective study of renal transplant outcomes obtained from the US Renal Data System occurring in 1990-2010 in 21,814 women of child-bearing age with (N = 729) and without pregnancies (N = 21,085) demonstrated a significantly higher rate of graft failure in those who conceived within two years of transplantation.[16] Only women who conceived after three years had comparable rates of graft loss to those women who did not have pregnancies.[16] Cessation of mycophenolate mofetil at least three months prior to pregnancy is desired to avoid teratogenicity, but the effect of switching to azathioprine on long-term graft function in those wishing to conceive within two years of transplantation requires further study because there is likely a complex interplay between pregnancy timing, maternal age, and existing comorbidities. The American Society of Transplantation guidelines for timing of conception[17] are outlined in Figure 1.

CONTRACEPTION

Contraception counseling is an essential part of pregnancy planning; however, a Brazilian study of female transplant recipients reported that contraception recommendations were made more commonly before transplantation than after, with only 49% of women having discussed contraception with their physician despite 80% being sexually active.[17] There frequently is uncertainty regarding contraceptive safety and efficacy in women with renal transplants in relation to immunosuppression and vascular risk. Estrogen can increase blood levels of immunosuppressants and should be avoided in those with hypertension, vascular disease, in smokers, and persons with diabetes because of the increased risk for thrombotic stroke and myocardial infarction.[19] Depot medroxyprogesterone acetate is not recommended in women with low bone mineral density.[20] There is no evidence that intrauterine devices are less effective due to immunosuppression[21] or are associated with increased risk for pelvic inflammatory disease. Nonetheless, assessment for gonorrhea and chlamydia is suggested before insertion.[22]

Recommendation
• No rejection in the previous year
• Adequate and stable renal function (e.g. serum creatinine <1.5 mg/dl) with no or minimal proteinuria
• No acute fetotoxic infections, e.g., cytomegalovirus
• Stable kidney function with non-teratogenic maintenance immunosuppression
• Additional factors which should be taken into consideration include: ▪ Rejection within the first year ▪ Maternal age ▪ Comorbid factors that may affect pregnancy and graft function ▪ Established medical noncompliance

Figure 1. Recommendations of the American Society of Transplantations to follow before Conception.[18]

MEDICATION BEFORE, DURING, AND AFTER PREGNANCY

An overview of medication safety during pregnancy and lactation is outlined in Table 1.[23,24] Frequently conflict arises regarding manufacturers recommendations for pregnancy and breast-feeding, which invariably suggest that medications should be avoided because of the lack of robust safety data. However, the danger of ceasing immunosuppression and other medications during pregnancy usually far outweighs any potential risk of fetotoxicity and needs to be carefully explained to women with renal transplants.

Important principles of prescribing immunosuppression in women with renal transplants during pregnancy include the following:

- Tacrolimus, cyclosporine, azathioprine, and prednisolone are all considered to be safe during pregnancy and breast-feeding.
- Mycophenolate mofetil is teratogenic and should be stopped at least three months before pregnancy to ensure graft stability on alternative agents.
- Azathioprine is a preferred alternative to mycophenolate mofetil and has an excellent safety profile in pregnancy and breast-feeding, despite being classified as Food and Drug Administration category D because of its teratogenicity in animals. However, only two cases of congenital abnormalities have been reported after several decades of use in pregnancy.
- The pharmacokinetics of calcineurin inhibitors are altered during pregnancy; lower blood concentrations often occur.[25] Dose adjustments (by 20%-25% or more) are frequently necessary to achieve the target concentrations, but caution should be used because preliminary data suggest that free tacrolimus concentrations might be higher in pregnant than in nonpregnant women.[26]

PREGNANCY OUTCOMES

In general, pregnancy outcomes in women with renal transplants are better than those on dialysis, although a