Fertility problems in kidney transplant recipients

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Chronic kidney disease (CKD) affects up to 6% of women of childbearing age. These patients often face fertility issues and low pregnancy rates due to hypothalamic-pituitary-ovarian axis disorders, but the ability to concieve significantly improves following a kidney transplant. The first successful pregnancy in a kidney transplant recipient occurred in 1958 to a 23-year-old woman who received a graft from her identical twin sister. Nine years later, this case was followed by a first successful pregnancy in an anovulating transplant patient. Current data show an unadjusted pregnancy rate during the first three post-transplant years of 33/1,000 women, which is three times lower than in the general population.

Preconception care

Pregnancy in transplant recipients is quite challenging due to the risk of maternal and fetal complications. In most patients, fertility is gradually and fully restored 12 months following transplantation. The first posttransplant year is associated with the highest rate of pregnancy-and graft-related complications and infections. Therefore, preconception care is crucial and conception should be carefully planned no earlier than one year following transplantation, provided the graft function is stable, maintenance immunosuppressive therapy abated, and the risk for opportunistic infections reduced. The European Best Practice Guidelines suggest an even longer postponement of 2 years after transplantation in women with good renal function (serum creatinine <132.6 umol/L), no proteinuria, well-controlled blood pressure with pregnancy-appropriate medications, and with normal allograft ultrasound. Patients with viral infections, extreme age, obesity, significant comorbidities, chronic transplant rejection, an underlying disease with a high recurrence rate, a history of non-compliance, or exposure to mycophenolate or mTOR inhibitors should be addressed individually.

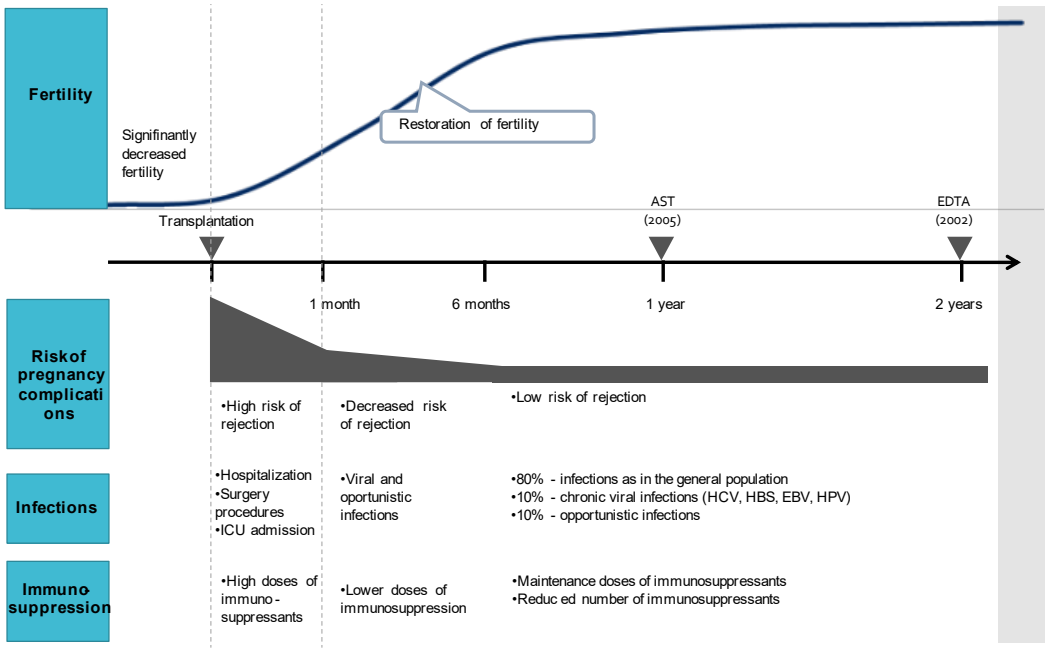

Figure 1. Timing of conception in kidney transplant recipients

Preparation for conception should include counseling and adjustment of immunosuppressive therapy and treatment of coexisting diseases to pregnancy-safe modalities. The preconception multidisciplinary counseling team should include an obstetrician, transplant physicians, and genetic counselor in case of known or suspected risk for inheritable diseases. Genetic testing can also be performed before transplantation in high-risk cases. Despite these recommendations, as many as half of the pregnancies in solid organ recipients are unplanned, and there are even case reports of conceiving immediately after transplantation, and also of transplantations performed during pregnancy.

Pregnancy care

Pregnancy in transplant recipients is always considered high-risk and should receive cautious prenatal care from a multidisciplinary team of perinatologists and transplant physicians. Prenatal visits should be more frequent with a regular screening of graft function, early screening for gestational diabetes (especially in patients on tacrolimus and/or prednisone), and careful assessment for early signs of preeclampsia. Low-dose aspirin (75mg -150mg) should be administered in all post-transplant pregnancies, especially with proteinuria and hypertension, to reduce the risk of preeclampsia. Oral labetalol and methyldopa and calcium channel blockers are considered first-line agents to treat hypertension. Both angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in pregnancy because of a significant association between overall and cardiovascular congenital malformations, miscarriage, and stillbirth with first-trimester exposure to these agents. They should therefore be discontinued at least 6 weeks before a planned pregnancy, along with mycophenolate mofetil and mTOR inhibitors which are associated with the ear, lip, and palate malformations, among others. On the other hand, corticosteroids, cyclosporine A, and tacrolimus are considered relatively safe. Azathioprine is also not contraindicated in pregnancy.

Intrapartum care

Normal vaginal delivery is probably the safest method of delivery in kidney transplant patients, and Cesarean section and forceps delivery should be performed only for strict obstetric indications. Nevertheless, current data show that half of the pregnant kidney transplant recipients, one-third of liver transplants, and even 57% of combined kidney and pancreas recipients are delivered by C-section, with no detailed explanation of the indications for this procedure.

For patients previously receiving corticosteroids, one stress dosage should be administered parenterally during the delivery, and the previous maintenance dose should be increased up to 50% after delivery. Antibiotics administration should rely on the same principles as in the general population, but the sanitary regime should be strengthened.

Pregnancy outcomes and complications

Renal recipients have a significantly higher risk of obstetric and neonatal complications compared to the general population. The risk for miscarriage in renal transplant recipients is as high as 40% in the first trimester but promptly drops to 10% in the second and third trimesters. Preterm delivery and low

birth weight are more common in transplant recipients than in the general population, but the incidence of birth defects is not higher. Neonatal infections and respiratory distress syndrome are also more common in transplanted patients, and neonatal outcomes are even worse in kidney than in liver recipients. Kidney recipients also have a significantly higher risk of obstetric complications compared to liver recipients, probably due to coexisting diseases. Stable allograft function is associated with better pregnancy outcomes. Thus, careful monitoring for infection, rejection and immunosuppressive dose adjustment is of utmost importance.

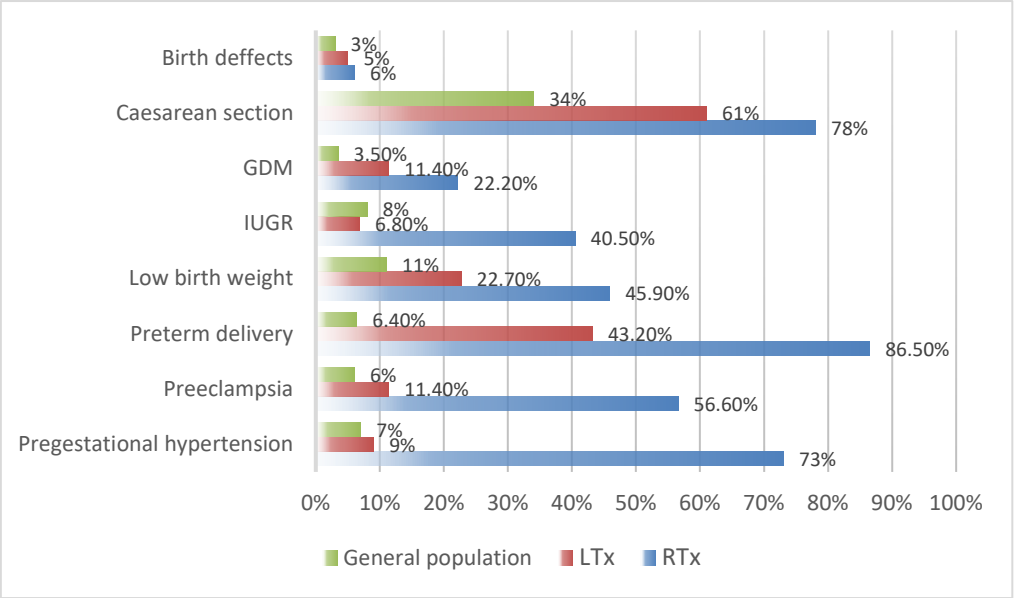

Figure 2. Pregnancy and neonatal complications in the general population and patients with kidney and liver transplants

Postnatal care

There are no definite guidelines on breastfeeding with immunosuppressive medications, but it is generally considered safe and is therefore encouraged. Even though all immunosuppressive agents cross to the mother's milk, infant exposure to drugs through breast milk is far less than in utero. Cyclosporine is detected in 0.1%, and everolimus in 0.38% of the maternal weight-adjusted dose in breast milk. Immunosuppressive treatment is not routinely increased in the peripartum period and dosing is based on clinical indications and drug blood levels. It is recommended to plan renal function testing in the early postpartum period.

In vitro fertilization and contraceptive measures

Assisted reproduction is an option for kidney transplant patients with fertility issues, but its performance does come as a challenge. Timing is of the utmost importance to ensure optimal results with minimum risk. The first successful pregnancy following in vitro fertilization and an embryo transfer in a kidney transplant recipient was recorded in 1995. Eligible patients should have stable graft function, adequate immunosuppression, and well-controlled blood pressure. The most common complications include preeclampsia and preterm delivery, intrauterine growth restriction, and gestational diabetes.

An adequate contraception method should be offered to transplanted women of reproductive age within one-year posttransplant and in case of graft rejection, but also to those taking teratogenic medication and with active glomerulonephritis. Uncomplicated kidney transplant recipients can initiate any contraceptive method, whereas complicated patients may use progestin contraceptives. The use of combined hormonal contraceptives (estrogen and progestin) is not well documented in transplant patients and should therefore be avoided. Insertion of a new intrauterine device is not advisable in complicated recipients, but a previously present device may remain.

Key points

1. Fertility is gradually and fully restored 12 months following transplantation, but pregnancies within this period are associated with multiple complications.
2. Conception should be discouraged in the first year post-transplantation and recipients of reproductive age should be offered an adequate contraceptive method.
3. Preparation for conception should include counseling and adjustment of immunosuppressive therapy and treatment of coexisting diseases to pregnancy-safe modalities.
4. There is no data to support preferential delivery by Cesarean section in transplanted patients.
5. The benefits of breastfeeding highly outweigh the potential risks and breastfeeding should be encouraged in transplant patients.

Further reading

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