Planned Pregnancy in Kidney Transplantation

Subjects: Urology & Nephrology

Contributor: Claudio Ponticelli

Pregnancy is not contraindicated in kidney transplant women but entails risks of maternal and fetal complications. Three main conditions can influence the outcome of pregnancy in transplant women: preconception counseling, maternal medical management, and correct use of drugs to prevent fetal toxicity.

Keywords: posttransplant pregnancy ; fetotoxicity ; eclampsia ; immunosuppression

1. Introduction

In most women with successful kidney transplantation, fertility is spontaneously restored within a few months, resulting in normal ovulatory cycles and regular menstruation [1][2][3]. This offers a chance for transplanted women to have children. Pregnancy can be a reasonable option for women with a good function of the kidney transplant. However, pregnancy in transplanted patients remains high risk [4]. A meta-analysis and systematic review of 6712 pregnancies in 4174 kidney transplant recipients reported that the live-birth rate was 72.9%. The other pregnancy outcomes were complicated by cesarean section (62.6%), preterm delivery (43.1%), pregnancy-induced hypertension (24.1%), preeclampsia (21.5%), miscarriages (15.4%), induced abortions (12.4%), gestational diabetes (5.7%), stillbirths (5.1%), and ectopic pregnancies (2.4%) [5].

2. Planning Posttransplant Pregnancy

Pregnancy leads to physiologic changes in kidney and systemic hemodynamics that cause important alterations in acid–base, electrolyte, and kidney function. Glomerular hyperfiltration occurs during pregnancy. An increase in 24 h creatinine clearance by 25% occurs in the first 4 weeks after the last menstrual period and by 45% at 9 weeks. During the third trimester, there is some decrease in creatinine clearance with a small increase in the first days of puerperium. An increase in plasma uric acid concentration in pregnancy may predict the development of preeclampsia. Proteinuria may develop in almost 40% of patients near term but disappears after delivery. Transient diabetes insipidus may occur late in pregnancy. It disappears with puerperium but may be responsible for hypovolemia and electrolyte unbalance [6]. Understanding these changes is essential when evaluating pregnant women with kidney transplantation, outlining that transplanted pregnant women should be closely monitored and followed by a team of expert nephrologists and gynecologists.

The potential issues of pregnancy should be discussed, preferably prior to transplantation, by women and their partners with a multidisciplinary team of expert nephrologists and obstetricians. Such issues include preconception counseling, knowledge of factors that may affect pregnancy success, the timing of pregnancy, and the possible impact of medical management on maternal and fetal outcomes [7][8].

Early counseling on contraception is important to reduce the risk of unplanned pregnancies, improve pregnancy outcomes, and reduce maternal complications. Hormonal methods may be safe in women with stable graft function but are not recommended in women with hypertension or risk of thrombosis. Indeed, arterial hypertension during pregnancy is associated with increased arterial thrombotic risk [9]. All combined oral contraceptives investigated in an analysis were associated with an increased risk of venous thrombosis; the effect size depended both on the progestogen used and the dose of ethinylestradiol [10]. Intrauterine devices, oral contraceptives, and subdermal implants have been shown to have great efficacy as well as low systemic drug absorption, allowing clinicians to provide a vast range of options to transplant women in their childbearing years [11][12][13]. Counseling should be repeated after transplantation [14]. Emergency contraception with high dose progestins or intrauterine devices is not contraindicated, but it should be avoided whenever possible, even if far preferable to abortion [15].

Several factors may affect pregnancy outcomes, including rejection, poor graft function, nephrotic syndrome, hypertension, obesity, diabetes, and infections. According to the National Transplantation Pregnancy Registry (NTPR), the ideal candidate for posttransplant pregnancy should not have had rejection in the last year, should have adequate and

stable kidney graft function (serum creatinine < 1.5 mg/dl and protein exception < 500 mg/24 h urine protein excretion), normal blood pressure (with or without therapy), and stable immunosuppression [8]. She should not suffer from comorbid factors that may worsen pregnancy outcomes, such as chronic allograft dysfunction, cardiopulmonary diseases, severe hypertension, diabetes mellitus, nephrotic proteinuria, morbid obesity, maternal infection with hepatitis B or C, and severe liver failure.

The timing of conception may depend on the characteristics of the patient. The NTPR suggested that a patient can safely proceed with the pregnancy, independently of the date of transplant, if graft function is optimal [8]. However, it can be unsafe to plan conception early after transplantation. The peritransplant period is a time of the highest use of potentially fetotoxic or teratogenic medications and a time when optimization of immunosuppression is essential to prevent rejection [16]. A retrospective study of 729 pregnancies revealed an increased risk of death-censored graft loss during the first and second year after transplantation (hazard ratio 1.25 and 1.26, respectively), while pregnancy in the third year was no longer associated with an increased risk of graft failure [17]. Thus, it is safer to plan pregnancy at least 2 years after transplantation [18][19][20].

The patient should be vaccinated before pregnancy. Most live attenuated vaccines are contraindicated after transplantation. Thus, women who are not immune to rubella should receive the rubella vaccine before transplantation. However, there are emerging safety profile and efficacy data to support the use of specific live attenuated vaccines. In the posttransplant setting, inactivated vaccines can be administered starting at 3 months posttransplant, except for influenza, which can be given as early as one month. Close contacts of transplant patients can receive most routine live vaccines, including pneumococcal, influenza, hepatitis B, human papilloma virus, and meningococcal vaccines. In general, vaccines are recommended more than two weeks prior to transplantation, or starting at 1-6 months after transplantation [21]. Of particular concern is coronavirus disease 2019 (COVID-19) which is associated with a high rate of hospitalization and admission to intensive care units in kidney transplant recipients [22][23][24][25]. Since persons on immunosuppressive medications are at increased risk for severe COVID-19, it is recommended that those people may receive a COVID-19 vaccine along with counseling that the vaccine safety and efficacy profiles are unknown, and there is a potential for reduced immune responses [26].

3. Maternal Medical Management and Outcomes during Pregnancy

The aims of the treatment are to maintain alloimmunity quiescence during and after pregnancy and to improve the outcome of the fetus. Reaching these goals largely depends on the conditions of the patient at conception. Besides the recommendations reported above, pregnancy should be avoided in women with acute rejection in the last 12 months before conception and in patients with impaired graft function. In pregnant women with various stages of CKD, the risk of adverse outcome increased from 34% to 90% from stage 1 to 4 [27]. In many cases, prematurity and low birth weight are caused by obstetric management to favor early delivery in patients with severe CKD or preeclampsia. In these cases, it is difficult to balance the interest of the pregnant woman and her fetus. Some authors have proposed that maternal autonomy should be the dominant concern in decision making, whereas others have established the fetus as a patient who should be treated according to the principles of beneficence.

The most frequent maternal risks include infection, hypertension, preeclampsia, gestational diabetes, and acute rejection (**Table 1**).

Table 1. Main maternal adverse events during pregnancy after kidney transplantation.

Complication	Incidence	Consequences
Infection	Very common. Urinary tract infection (often asymptomatic) may affect most transplant women.	Urinary tract infections can increase the risk of preeclampsia. Pyelonephritis is an uncommon but severe complication. The risk of viral infection is elevated in case of early pregnancy. Infection may lead to graft dysfunction.
Hypertension	Many transplanted women are already hypertensive before pregnancy.	Hypertension can predispose to preeclampsia and is a main risk factor for cardiovascular disease, cerebrovascular disease, and graft dysfunction.

Complication	Incidence	Consequences
Preeclampsia	The incidence is higher in patients with poor graft function or hypertension.	Preeclampsia may result in damage to the kidneys, liver, lung, heart, or eyes, and may cause a stroke or other brain injury.
Gestational diabetes mellitus	About 16%	A maternal and neonate risk factor of adverse events during pregnancy.
Acute rejection	About 10%	Risk factor for graft dysfunction. Infection may develop after aggressive immunosuppressive treatment.

4. Immunosuppressive Drugs and Fetal Outcome

A major issue is represented by the potential teratogenic or toxic effects on the fetus (**Table 2**). The immunosuppressive agents more frequently used in kidney transplantation may be divided into three main categories: drugs that are relatively safe, new drugs with uncertain safety, and drugs with moderate to high fetal risk (**Table 2**).

Table 2. Potential teratogenic effects of immunosuppressive drugs.

Glucocorticoids (GC)	GC can cross the placenta but are metabolized by 11 β-HSD2 to inactive products with the exception of dexamethasone and betamethasone. Fetal toxicity cannot be ruled out (Class C according to FDA).	Minimal risk of oral-facial cleft. It is unlikely that moderate doses of GC lead to fetal hypothalamic-pituitary-adrenal axis dysfunction or interfere with the early life programming, since 11β-hydroxysteroid dehydrogenase 2 is a major barrier against cortisol transfer to the fetus. Concern remains about the fetal toxicity when the mothers receive prolonged treatments with high-dose GC.
Calcineurin inhibitors (CNI)	CNI metabolites can be seen in the placenta. The CNI maternal–fetal transplacental passage is influenced by the activity of P-glycoprotein that pumps CNI out of the trophoblast cells of placenta and restricts its passage across the placental barrier. CNI are listed in Class C.	The relatively high number of premature births that has been reported may be partially explained by an obstetric policy favoring earlier delivery. Nonetheless, long-term effects in humans prenatally exposed to CNIs require further evaluation.
Azathioprine (AZA)	Placenta is a barrier to 6-mercaptopurine the main metabolite of AZA. This explains the lack of teratogenicity of AZA. The FDA classified AZA as a drug at potential risk of teratogenic effects (Class C) based on animal studies.	The risk of congenital anomalies in offspring are similar to those found in general population, but there is a higher incidence of prematurity and lower weight at birth in AZA-treated pregnant women. There is also an increased risk of materno-fetal infections, especially CMV infection. The use of AZA is considered safe.

Mycophenolic acid (MPA)	MPA during pregnancy is associated with an increased risk of congenital malformations. MPA is considered as class D (Evidence of risk to human fetus) by FDA.	Women being considered for treatment with MPA should always have a negative pregnancy test. There is an increased risk of pregnancy loss and congenital malformations with the use of MPA during pregnancy. If pregnancy occurs MPA should be stopped. The later MPA is discontinued the higher is the risk of complications.
mTOR inhibitors (mTORi)	Animal reproduction studies have shown an adverse effect on the fetus. There are not adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; mTORi are considered as class C by FDA.	The mTORi exposure during pregnancy does not appear to be associated with an increased risk or a pattern of birth defects.
Rituximab (RTX)	Data on RTX during pregnancy are scarce. RTX contains an IgG and can cross the placenta. RTX is considered in class C.	The administration of RTX to a pregnant woman is discouraged unless the benefits outweigh the potential risk for the fetus.
Eculizumab	There is a selective transport of unbound eculizumab across the placenta. However, the levels observed in umbilical cord blood samples do not affect the concentrations of complement in newborns.	The use of eculizumab to pregnant women with paroxysmal hemoglobinuria nocturnal is associated with a high rate of fetal survival and a low rate of maternal complications. Therefore, eculizumab may be regarded as safe in pregnancy.
Belatacept	There are not formal studies for the use of Belimumab in pregnant women.	Anecdotal cases of successful pregnancy with the use of belatacept in transplant women have been reported.

5. Conclusions

Pregnancy is not contraindicated in transplant women, but it should be planned with an obstetrician and nephrologist. Ideally, the patient should not become pregnant 1-2 years after transplantation and should have normal blood pressure and kidney function. The maternal risks include hypertension, preeclampsia, thrombotic microangiopathy, graft dysfunction, gestational diabetes, and infection. The main fetal risks include prematurity, low birth weight, and abortion, particularly in patients with poor graft function. Renin–angiotensin system inhibitors and some immunosuppressive agents, such as mycophenolate, bortezomib, and cyclophosphamide, are teratogenic and should not be prescribed to pregnant women. If these recommendations are respected, pregnancy can be considered a safe option in kidney transplant women.

References

1. Pezeshki, M.; Taherian, A.A.; Gharavy, M.; Ledger, W.L. Menstrual characteristics and pregnancy in women after renal transplantation. Int. J. Gynaecol. Obstet. 2004, 85, 119–125.
2. Rao, S.; Ghanta, M.; Moritz, M.J.; Constantinescu, S. Long-Term Functional Recovery, Quality of Life, and Pregnancy After Solid Organ Transplantation. Med. Clin. N. Am. 2016, 100, 613–629.
3. Sarkar, M.; Bramham, K.; Moritz, M.J.; Coscia, L. Reproductive health in women following abdominal organ transplant. Am. J. Transpl. 2018, 18, 1068–1076.

4. Piccoli, G.B.; Cabiddu, G.; Attini, R.; Gerbino, M.; Todeschini, P.; Perrino, M.L.; Manzione, A.M.; Piredda, G.B.; Gnappi, E.; Caputo, F.; et al. Outcomes of Pregnancies After Kidney Transplantation: Lessons Learned From CKD. A Comparison of Transplanted, Nontransplanted Chronic Kidney Disease Patients and Low-Risk Pregnancies: A Multicenter Nationwide Analysis. Transplantation 2017, 101, 2536–2544.
5. Shah, S.; Venkatesan, R.L.; Gupta, A.; Sanghavi, M.K.; Welge, J.; Johansen, R.; Kean, E.B.; Kaur, T.; Gupta, A.; Grant, T.J.; et al. Pregnancy outcomes in women with kidney transplant: Metaanalysis and systematic review. BMC Nephrol. 2019, 20, 24.
6. Davison, J.M.; Baylis, C. Pregnancy in patients with underlying renal disease. In Oxford Textbook of Clinical Nephrology; Davison, A.M., Cameron, J.S., Grunfeld, J.P., Ponticelli, C., Ritz, E., Winearls, C.G., van Ypersele, C., Eds.; Oxford University Press: Oxford, UK, 2005; Volume 3, pp. 2243–2259.
7. McKay, D.B.; Josephson, M.A.; Armenti, V.T.; August, P.; Coscia, L.A.; Davis, C.L.; Davison, J.M.; Easterling, T.; Friedman, J.E.; Hou, S.; et al. Reproduction and transplantation: Report on the AST Consensus Conference on Reproductive Issues and Transplantation. Am. J. Transpl. 2005, 5, 1592–1599.
8. Coscia, L.A.; Constantinescu, S.; Moritz, M.J.; Frank, A.M.; Ramirez, C.B.; Maley, W.R.; Doria, C.; McGrory, C.H.; Armenti, V.T. Report from the National Transplantation Pregnancy Registry (NTPR): Outcomes of pregnancy after transplantation. Clin. Transpl. 2010, 65–85.
9. Scheres, L.J.J.; Lijfering, W.M.; Groenewegen, N.F.M.; Koole, S.; de Groot, C.J.M.; Middeldorp, S.; Cannegieter, S.C. Hypertensive Complications of Pregnancy and Risk of Venous Thromboembolism. Hypertension 2020, 75, 781–787.
10. Stegeman, B.H.; de Bastos, M.; Rosendaal, F.R.; van Hylckama Vlieg, A.; Helmerhorst, F.M.; Stijnen, T.; Dekkers, O.M. Different combined oral contraceptives and the risk of venous thrombosis: Systematic review and network meta-analysis. BMJ 2013, 347, 5298.
11. Paulen, M.E.; Folger, S.G.; Curtis, K.M.; Jamieson, D.J. Contraceptive use among solid organ transplant patients: A systematic review. Contraception 2010, 82, 102–112.
12. Yousif, M.E.; Bridson, J.M.; Halawa, A. Contraception After Kidney Transplantation, From Myth to Reality: A Comprehensive Review of the Current Evidence. Exp. Clin. Transpl. 2016, 14, 252–258.
13. Huguelet, P.S.; Sheehan, C.; Spitzer, R.F.; Scott, S. Use of the levonorgestrel 52-mg intrauterine system in adolescent and young adult solid organ transplant recipients: A case series. Contraception 2017, 95, 378–381.
14. Chandra, A.; Midtvedt, K.; Asberg, A.; Eide, I.A. Immunosuppression and Reproductive Health After Kidney Transplantation. Transplantation 2019, 103, e325–e333.
15. Attini, R.; Cabiddu, G.; Montersino, B.; Gammaro, L.; Gernone, G.; Moroni, G.; Santoro, D.; Spotti, D.; Masturzo, B.; Gazzani, I.B.; et al. Contraception in chronic kidney disease: A best practice position statement by the Kidney and Pregnancy Group of the Italian Society of Nephrology. J. Nephrol. 2020, 33, 1343–1359.
16. McKay, D.B.; Josephson, M.A. Pregnancy after transplantation. Clin. J. Am. Soc. Nephrol. 2008, 3 (Suppl. 2), S117–S125.
17. Rose, C.; Gill, J.; Zalunardo, N.; Johnston, O.; Mehrotra, A.; Gill, J.S. Timing of pregnancy after kidney transplantation and risk of allograft failure. Am. J. Transpl. 2016, 16, 2360–2367.
18. 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. Transpl. 2002, 17 (Suppl. 4), 50–55.
19. Davison, J.M.; Bailey, D.J. Pregnancy after transplantation. J. Obstet. Gynaecol. Res. 2003, 29, 227–233.
20. Cabiddu, G.; Spotti, D.; Gernone, G.; Santoro, D.; Moroni, G.; Gregorini, G.; Giacchino, F.; Attini, R.; Limardo, M.; Gammaro, L.; et al. A best-practice position statement on pregnancy after kidney transplantation: Focusing on the unsolved questions. The Kidney and Pregnancy Study Group of the Italian Society of Nephrology. J. Nephrol. 2018, 31, 665–681.
21. Danziger-Isakov, L.; Kumar, D. AST ID Community of Practice. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. Clin. Transpl. 2019, 33, e13563.
22. Zhu, L.; Gong, N.; Liu, B.; Lu, X.; Chen, D.; Chen, S.; Shu, H.; Ma, K.; Xu, X.; Guo, Z.; et al. Coronavirus Disease 2019 pneumonia in immunosuppressed renal transplant recipients: A summary of 10 confirmed cases in Wuhan China. Eur. Urol. 2020, 77, 748–754.
23. Banerjee, D.; Popoola, J.; Shah, S.; Ster, I.C.; Quan, V.; Phanish, M. COVID-19 infection in kidney transplant recipients. Kidney Int. 2020, 97, 1076–1082.

24. Alberici, F.; Delbarba, E.; Manenti, E.; Econimo, L.; Valerio, F.; Pola, A.; Maffei, C.; Possenti, S.; Zambetti, N.; Moscato, M.; et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney Int. 2020, 97, 1083–1088.
25. Caillard, S.; Chavarot, N.; Francois, H.; Matignon, M.; Greze, C.; Kamar, N.; Gatault, P.; Thaunat, O.; Legris, T.; Frimat, L.; et al. Is COVID-19 infection more severe in kidney transplant recipients? Am. J. Transpl. 2021, 21, 1295–1303.
26. Tillett, R.L.; Sevinsky, J.R.; Hartley, P.D.; Kerwin, H.; Crawford, N.; Gorzalski, A.; Laverdure, C.; Verma, S.C.; Rossetto, C.C.; Jackson, D.; et al. Genomic evidence for reinfection with SARS-CoV-2: A case study. Lancet Infect. Dis. 2021, 21, 52–58.
27. Piccoli, G.B.; Cabiddu, G.; Attini, R.; Vigotti, F.N.; Maxia, S.; Lepori, N.; Tuveri, M.; Massidda, M.; Marchi, C.; Mura, S.; et al. Risk of Adverse Pregnancy Outcomes in Women with CKD. J. Am. Soc. Nephrol. 2015, 26, 2011–2022.