editing in which organogenesis has been disabled. This created an environment facilitating the enrichment of rat pluripotent stem cell derivatives in the tissues of mice. However, naïve rodent pluripotent stem cells were not found to be able to contribute to chimera formation in pigs. Moving to human pluripotent stem cells, the authors show that these cells were able to engraft in pig and cattle preimplantation blastocysts, although they did not contribute significantly to the postimplantation embryos and thus did not form efficient chimeras. Culturing of the human stem cells under specific conditions, the authors were able to create an intermediate pluripotent stem cell type, which interestingly resulted in higher levels of chimerism and progeny development in postimplantation pig embryos. Whether this degree of chimerism results in successful human-pig blastocyst complementation and subsequent organ development is not yet clear. Although promising, the approach is still considerably inefficient, and further work will need to address methods for creating a selective advantage for human pluripotent stem cells in recipient species.

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Selective Graft-Versus-Leukemia Depends on Magnitude and Diversity of the Alloreactive T-Cell Response

van Bergen CAM, van Luxemburg-Heijs SAP, de Wreede LC, et al. *J Clin Invest*. 2017;127(2):517–529.

Allogeneic stem cell transplants for the treatment of hematological malignancies result in a fine balance between graft-versus-leukemia (GVL) and graft-versus-host (GVH) responses. While GVL effects are necessary for the destruction of malignant cells, GVH may be initiated by the same transplanted T cells that mediate the GVL reactivity. While removing T cells from the stem cell transplant reduces the risk of GVH, it negatively impacts the GVL effect. In patients receiving a T cell-depleted transplant, or in patients experiencing a recurrence, a later donor lymphocyte infusion (DLI) may be used to eliminate any persisting malignant cells. Interestingly, a T cell depleted stem cell transplant followed by a DLI results in lower GVH incidence than a non–T cell–depleted transplant without a DLI. As DLIs are given late after chemotherapy, the reduction in GVH incidence may be secondary to reduced allorecognition in a noninflamed environment. Van Bergen and coworkers from Leiden investigated the magnitude and diversity of the alloreactive CD8 T-cell response in patients who responded to DLI after receiving a T cell-depleted stem cell transplant.[1] Cells were isolated and clonally expanded from patients, then analyzed for their reactivity against both hematopoietic and nonhematopoietic cells. In patients who had a GVL but not a GVHD response, there were fewer CD8 T cells with specificity for minor histocompatibility antigens. These cells showed a low reactivity against nonhematopoietic cells and overall lower diversity in TCR-β repertoires. In addition, alloreactive CD8 T cells maintained low reactivity even when treated with inflammatory cytokines. Conversely, in patients who had developed GVHD, CD8 alloreactivity was of a higher magnitude and diversity, with increased reactivity directed to widely expressed minor histocompatibility antigens. The authors suggest that the main determinant that separates GVL reactivity from GVH reactivity is an inflamed environment initiating a GVHD response in T cells that would normally not be alloreactive if conditions were noninflammatory. These data therefore provide a rationale for novel treatments including strategies for selecting T cells for DLI that are restricted to only hematopoietic (and not nonhematopoietic) minor histocompatibility antigens.

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eResources

Pregnancy After Renal Transplantation

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In 2016, 17 332 kidney transplantations were performed in the United States. Of the 6855 female recipients, 2767 (40.3 %) were of childbearing age (18-49 years). Additionally, 296 recipients were minors (≤17 years) who might become pregnant later in life [A]. Reliable, publicly accessible information about pregnancy in kidney transplant recipients, including maternal and fetal risks, as well as recommendations on management of pregnancies in these "high risk" patients, is sparse and occasionally outdated. This article collates online resources with relevance to the readership of *Transplantation* providing an up-to-date view on pregnancy outcomes after kidney

transplantation including potential complications for the recipient and the unborn child in addition to the management of renal transplant recipients during pregnancy.

Due to loss of libido, anovulatory vaginal bleeding or amenorrhea linked to high prolactin levels,[1] women of childbearing age on renal replacement therapy have nearly tenfold lower fertility rates compared to the general population.[2] Nevertheless, a very recent meta-analysis showed that the number of successful pregnancies in patients with end stage renal disease has substantially increased. Compared to 90 pregnancies reported amongst women on hemodialysis between 2000 and 2008, a total of 464 cases were reported from 2009 to 2014. Although reporting bias may partially explain this remarkable increase, it emphasizes the growing interest in pregnancy on dialysis and the medical achievements over the last years which lead to profoundly improved pregnancy outcomes in these patients; in particular, more effective dialysis regimens in pregnant women has been cited as an important factor contributing to increased pregnancy rates.[3] Although successful pregnancies in women on hemodialysis can be achieved, fertility rates are much higher after renal transplantation with hormonal functions returning quickly after transplantation: Ovulatory cycles can begin within 4 weeks after transplantation and on average, menstruation becomes regular by 6.9 months.[4] Normal levels of circulating sex steroids are typically restored within 6 months.[5,6]

The bulk of information on pregnancies in kidney transplant recipients is based on case reports, a few reviews,[4,5] single-center studies and 4 voluntary registries: the National Transplantation Pregnancy Registry (NTPR) in the US[7] [B], the European Dialysis and Transplant Association registry [C], the UK Transplant Pregnancy Registry[8] and the Australia and New Zealand Dialysis and Transplant registry (ANZ-DATA)[9] [D]. In the most recent meta-analysis from 2011, a total of 4706 pregnancies in 3570 kidney transplant recipients were reported from 2000 to 2010[10] with a live birth rate consistently between 72% and 80%,[7,9-11] a rate that is comparable to the general population. However, renal transplant recipients experience overall higher rates of cesarean sections, preterm (<37 weeks) deliveries with babies of small gestational age and low birth weight.[9,10] Similar outcomes are registered for pregnant mothers who received a transplant as a minor.[12]

Pregnancies in renal transplant recipients are considered "high risk" because mother and offspring may experience complications related to their underlying diseases, suboptimal allograft function and immunosuppressive therapy. Potential maternal complications include hypertension or preeclampsia, deterioration of graft function and urinary tract infections. The unborn child is susceptible to drug toxicity and congenital infections.

Hypertension/Preeclampsia

Arterial hypertension in kidney transplant recipients is common before and during pregnancy, occurring with an incidence of 52 to 73 %.[5,8,10,11] Preeclampsia occurs in about one-third of kidney transplant recipients (21-38%), compared to a risk of 4% in the general population.[5,7,8,10] Hypertension and preeclampsia are the 2 main reasons for the high rate of preterm babies in kidney transplant recipients.[5] The antihypertensive agent of choice is methyldopa, followed by α- and β-adrenergic blockers, calcium-channel blockers and thiazides. Inhibitors of the RAAS system have been linked to fetopathies and are contraindicated after the first trimester[5] [E, F, G].

Links
[A] https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/
[B] https://www.transplantpregnancyregistry.org/
[C] https://www.era-edta-reg.org/index.jsp?p=1
[D] http://www.anzdata.org.au/
[E] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[F] https://www.medicines.org.uk/emc/medicine/1680#PREGNANCY
[G] http://www.embryotox.de/einfuehrung.html
[H] https://www.mycophenolaterems.com/PregnancyRegistry.aspx
[I] http://kdigo.org/home/guidelines/care-of-the-kidney-transplant-recipient/
[J] http://renalfellow.blogspot.de/2013/12/pregnancy-in-kidney-transplant.html
[K] https://www.kidney.org/transplantation/transaction/TC/Summer13/Having-Children-after-Transplant
[L] https://transplantliving.org/after-the-transplant/pregnancy/

Graft Outcome and Rejection

Three prepregnancy factors are highly associated with graft loss or decline in kidney function during pregnancy: a history of drug-treated hypertension, elevated serum creatinine levels and proteinuria. Registry data and single-center results clearly demonstrate that pregnancy itself has no impact on graft function in absence of these risk factors. Several studies analyzing long-term graft outcomes in kidney transplant recipients with a history of pregnancy compared to nulliparous controls showed there no difference in kidney function at years 1, 5, and 10 and comparable graft survival rates after 15 years (61.6-67.3% vs 58.1-68.7%).[4] Acute rejection rates during pregnancies and in the first 3 months postpartum ranged between 9% and 14.5%, comparable to controls.[5,13] It is presently unknown how exposure to fetal alloantigens during pregnancy affects graft-directed alloimmune responses. One might imagine that immunoregulatory mechanisms preventing the rejection of the allogeneic fetus could also prevent the graft from being rejected during pregnancy. On the other hand, it is well-known that pregnancies prior to transplantation represent a highly sensitizing event leading to development of anti-HLA antibodies, which is strongly associated with increased graft loss.[14] It is not known whether inheritance of paternal alloantigens by the fetus that happen to be shared with the transplanted organ influence graft function or survival; hence, current guidelines make no recommendations about HLA typing and risk-stratification of prospective fathers.

Other Maternal Complications

Urinary tract infections in female transplant recipients are common and the risk increases during pregnancies up to 40 %, possibly related to a dilatation of ureters and renal collecting

ducts.[15] There are conflicting observations about rates of gestational diabetes in different cohorts of pregnant kidney transplant recipients, but if any, there seems to be only a slightly increased risk for developing diabetes during pregnancy.[8,10]

Consequences of Immunosuppression for the Unborn Child

Calcineurin inhibitors (mostly tacrolimus) and mycophenolic acid (an antiproliferative agent) with or without prednisone constitute the most commonly used immunosuppressive regimen in kidney transplant recipients.[16] Each of these different agents passes the placenta and can be found in fetal circulation.[15] Therefore, special attention must be paid to potential teratogenic side effects [G].

Compared with cyclosporine there are fewer data on the impact of tacrolimus in pregnancy. A meta-analysis of 100 pregnancies in 84 women with transplants treated with tacrolimus showed an increased rate of preterm deliveries, but birth weight was appropriate for gestational age in most cases. Complications of tacrolimus therapy during pregnancy for mothers include treatment failure resulting in transplant rejection, preeclampsia, renal impairment and infection. Thirty-three percent of neonates born to tacrolimus-treated mothers experienced 1 or more complications, albeit transient and reversible, most frequently hypoxia, hyperkalemia or renal dysfunction.[17] The rate of congenital malformations after gestational exposure to tacrolimus was not higher than in the general population; therefore, tacrolimus is graded as safe in pregnancy and should be continued [F, G].

The teratogenic effects of mycophenolic acid are well known from preclinical studies in rabbits and rats. Retrospective analysis of registry data, case, and series reports, in addition to a prospective study, confirmed that mycophenolic acid is similarly toxic in human fetal development.[18] Consistently higher rates of miscarriages (42-52% vs 19%) and birth defects (16-23% vs 6%) were recorded among female kidney transplant recipients exposed to mycophenolic acid compared to women who discontinued the drug prior to conception [H]. Although developmental malformations are manifold, a specific embryopathy pattern under first trimester exposure to mycophenolic acid has been described, characterized by microtia, orofacial clefts, coloboma, hypertelorism, micrognathia, congenital heart defects, agenesis of the corpus callosum, esophageal atresia, and digital hypoplasia.[19] KDIGO guidelines for the care of kidney transplant recipients recommend switching patients from mycophenolic acid to azathioprine 6 weeks before attempted conception or as soon as possible after an unplanned pregnancy has been confirmed[20] [I].

Animal studies have associated exposure to sirolimus with decreased fetal weight and delayed ossification of skeletal structures. When administered to pregnant animals in combination with cyclosporine, increased fetal mortality, increased numbers of resorptions and decreased numbers of live fetuses were reported, suggesting an augmented toxicity of sirolimus in conjunction with CNI treatment.[21] Safety information about fetal exposure to mTOR inhibitors in humans remains sparse. Despite a number of case reports of successful pregnancy in sirolimus- or everolimus-treated kidney transplant recipients, KDIGO guidelines advise against the use of mTOR inhibitors in pregnant patients [I].

Congenital Infections

Intrauterine exposure to immunosuppressive agents causes characteristic changes in the immunological profile of infants born to kidney transplant recipients, including lower numbers of $CD4^+$ T cells, activated $CD8^+$ T cells, NK cells and regulatory T cells, as well as a dramatic reduction in B cell numbers.[22] Despite these changes, the rate of congenital infections in babies of transplant recipients is not generally higher than in those born to nontransplanted mothers. A very recent retrospective analysis of 71 neonates born to transplant recipients (liver and kidney) showed no difference compared to general population.[23] Nevertheless, the risk of a clinically important primary or secondary CMV infection is increased in newborns of transplant recipients, especially in high-risk constellations (donor CMV positive/recipient CMV negative). Around one-third (30-39%) of primary CMV infections during pregnancy are transferred to the fetus and up to 13% of these cases results in a symptomatic congenital CMV infection in the newborn.[24]

The nephrological management of pregnancies after kidney transplantation entails 3 main responsibilities, namely, advising patients about the risks and optimal timing of pregnancy, managing maintenance immunosuppression before and during pregnancy, and treatment of renal complications (please see chapter 25 of guidelines issued by KDIGO for the care of pregnant kidney transplant recipients) [I].

Timing of Pregnancy After Kidney Transplantation

The optimal interval between transplantation and pregnancy remains a topic of debate. Current guidelines in the United States recommend conceiving only after the first year posttransplantation,[25] whereas waiting for 2 years after transplantation is recommended in Europe.[13] A recent retrospective study of 729 pregnancies in kidney transplant recipients from 1990 to 2010 revealed an association between a first-year pregnancy and increased risk of allograft failure from any cause (hazard ratio, 1.18). Pregnancies in the second year posttransplantation were associated with a significantly increased risk of death-censored graft loss (hazard ratio, 1.25), even after adjustment for differences in age, race, cause of end stage renal disease, donor type, duration of pretransplant dialysis, maintenance immunosuppression, HLA match, peak panel reactive antibodies, and calendar year of transplantation.[26]

Maintenance Immunosuppression

Current practice is to avoid the use of mycophenolic acid or mTOR inhibitors during pregnancy. There is no specific guidance on changes to tacrolimus, azathioprine or steroid therapy during pregnancy. However, with changes in fluid distribution and extracellular volume during gestation, it may be advisable to monitor levels of immunosuppressive drugs frequently throughout pregnancy. In case of acute rejections, methylprednisolone is the treatment of choice; for other agents, there is little information available.

CONCLUSIONS

Becoming pregnant is a very relevant, important and emotive topic for many patients of childbearing age undergoing kidney transplantation. There are some valuable, patient-orientated online sources of information about pregnancy after transplantation [J, K, L]. However, there is also much misleading information, which is not evidence-based or up-to-date.

Therefore, it is vital for transplant physicians to remain abreast of developments in the field and to actively counsel patients about fertility and contraception after transplantation.

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Special Article

The Opioid Crisis and Its Consequences

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THE OPIOID EPIDEMIC

Opioid-related morbidity and mortality has reached epidemic levels in the United States, with tragic results.[1] Since 2000, the national age-adjusted drug overdose rate has more than doubled, from 6.2 per 100 000 persons in 2000, to 14.7 per 100 000 in 2014.[2] In 2015, there were over 33 000 deaths attributed to opioid overdose in the United States, an increase of nearly 5000 compared with the previous year.[3,4] For the first time, drug overdose has surpassed firearms and motor vehicle trauma as the most common cause of accidental death among adults.[4] Most strikingly, the overall life expectancy in the United States has dropped for the first time since 1993, particularly for those under age