Review

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Immunosuppression and Reproductive Health After Kidney Transplantation

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Abstract. Following successful kidney transplantation, recipients usually regain fertility. Post-engraftment pregnancies should be planned and the teratogenic mycophenolic acid should be replaced with azathioprine before conception. To avoid unintentional pregnancies, pre-conception counseling is mandatory in women of reproductive age who are scheduled for a kidney transplant. Counseling should be repeated after transplantation. Female recipients should receive advice to use long-acting reversible contraception and avoid pregnancy for a minimum of 1 year following transplantation. Conception should be deferred even longer in female recipients with moderate to severe proteinuria, uncontrolled hypertension or reduced graft function and be very carefully discussed in highly HLA-sensitized patients. The recipient wishes, values and acceptance of pregnancy-related risk should receive attention. Assisted fertilization increases the risk of pre-eclampsia, but still result in live births. Pregnancy management in kidney transplant recipients should be provided by a multidisciplinary team consisting of a nephrologist, a midwife and an obstetrician with expertise in high-risk pregnancies. Until measurement of unbound fraction of calcineurin inhibitors becomes clinically available, we recommend to adjust calcineurin inhibitor dose according to whole blood trough level, even though it overestimates the effective drug concentration during pregnancy. If nephrotoxicity is suspected, the calcineurin inhibitor dose should be reduced. Breastfeeding should be accepted after kidney transplantation since infant immunosuppressive drug exposure via breastmilk is extremely low. The prevalence of congenital malformations in children fathered by male recipients, including patients on mycophenolic acid therapy at the time of conception, is at level with the general population.

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INTRODUCTION

Kidney transplantation reduces morbidity and mortality, improves quality of life and restores sexual function and fertility in most patients with end-stage renal disease.[1] Historically, female kidney transplant recipients (KTRs) were advised not to become pregnant, due to concern for maternal, graft, and fetal health.[2] Since pregnant women are excluded from immunosuppressive drug trials, safety data in KTR pregnancies are limited to animal studies and slowly accumulating epidemiological data, mainly from voluntary registries, plus case series and retrospective single-center cohort studies. Thus, recommendations for use of immunosuppressive drugs in pregnant KTRs are established with a rather low level of proof.[3] Epidemiological data suggest a high likelihood of successful KTR pregnancy outcomes, especially for women on mycophenolic acid (MPA) free regimens who conceive beyond the first year post-transplant.[4-6] In this review, we will address some unresolved issues and uncertainties concerning immunosuppressive therapy and reproductive health in KTRs.

FERTILITY

Renal insufficiency inhibits gonadal function, thus most men and women with end-stage renal disease are infertile.[7] During the first few months after kidney transplantation, sex hormone levels tend to normalize, sexual function improve, menstruation returns in female KTRs, motile sperms are produced in male KTRs and fertility is restored in the majority of patients.[7] Therefore, we strongly recommend that pre-conception counseling becomes mandatory in female recipients of reproductive age.[3,8] We also recommend physicians to provide pre-conception counseling for all young- and middle-aged female and male patients scheduled for a kidney transplant, to repeat counseling in the early post-transplant phase and thereafter provide annual counseling for women of reproductive age. Some

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frequent questions during pre-conception counseling are given in Table 1. The counseling should also address the fact that some recipients remain infertile due to antiviral or immunosuppressive drugs side-effects[9-17] and non-pharmacological causes,[7,18,19] as presented in Table 2.

FATHERHOOD

MPA is teratogenic.[20] Paternal MPA exposure at the time of conception could theoretically pose a threat to the unborn child; thus the European Medicines Agency recommend that sexually active men on MPA should use a barrier contraceptive method and advice their female partners to use highly effective contraception.[21] This is, however, not supported by epidemiological data or theoretic pharmacological calculations.

Jones et al (n = 152 pregnancies, United States) reported a 94% live birth rate fathered by male solid organ transplant recipients on MPA therapy at the time of conception. There were 11% preterm deliveries, which is more frequent than in the general population, but only 3% congenital malformations, similar to the general population.[22] Morken et al (n = 474 pregnancies, Norway) reported that pre-eclampsia was more frequent in pregnancies fathered by transplant

TABLE 1.

Frequent questions asked by recipients during preconception counseling

Fertility	Can I expect improvement of libido/menstruation/erection/fertility?
	Does immunosuppressive drug therapy adversely affect sexual function and fertility?
Fatherhood	What is the risk of fetal adverse effects/congenital malformations from parental immunosuppressive drug exposure?
Pregnancy	When is it safe to become pregnant after transplantation and what contraceptive method should be used in the meantime?
	What immunosuppressive drugs are considered safe in pregnancy?
	Will pregnancy/adjustment of immunosuppressive regimen affect the risk of rejection and short- and long-term graft function?
	What is the risk of maternal disease/obstetric complication during pregnancy?
	What is the risk of congenital malformation and miscarriage?
	What is the risk of adverse pregnancy outcomes in highly HLA-sensitized patients?
	Is assisted fertilization possible after transplantation?
	What is the role of the transplant nephrologist and the obstetrician during pregnancy management?
Breastfeeding	Does the infant get exposed to immunosuppressive drugs during breastfeeding?

HLA, human leukocyte antigen.

TABLE 2.

Pharmacological and non-pharmacological factors that may affect fertility after kidney transplantation

A. Drug	Comment	
CS	No effect	9
CNI	No effect	9
MPA	Rodent studies show no effect on fertility. Very limited data in humans	10
AZA	No effect	9
mTORi	Hypogonadism with high levels of FSH and LH and low levels of testosterone. Rodent studies show inhibition of mTOR mediated P70S6K phosphorylation, leading to reduced spermatogonial proliferation. Consequently, oligospermia after 4 wk and azoospermia after 3 mo exposure. In male KTRs, less motile spermatozoa, lower sperm count, and lower pregnancy rate. Sperm count was reversed after sirolimus discontinuation. Recovery of spermatogenesis after long-term therapy has not been studied to date. In female KTRs, increased prevalence of hypogonadism, dysmenorrhea, ovarian cysts, and infertility	11-14
Belatacept	Rodent study showed no effect on fertility. Very limited data in humans	15
Basiliximab	Very limited data	15
Rituximab	Rodent studies showed no effect on fertility. Very limited data in humans.	10,16
ATG	Very limited data.	15
Antiviral	Possible testicular damage.	17
B. Non-pharmacological	Comment	
Renal dysfunction	Inhibition of the hypothalamic-pituitary-gonadal axis, with high levels of circulating FSH, LH and prolactin and low levels of sex hormones, which leads to infertility and loss of libido in both sexes, erectile dysfunction in male KTRs and reduced vaginal lubrication, inability to achieve orgasm, oligo- or amenorrhea in female KTRs.	7
Uremic toxins	Germinal aplasia and destruction of seminiferous tubules in male KTRs, which may not be completely reversed even if renal function is normalized.	18
Dialysis vintage	Epididymal calcification and microlithiasis, obscuring the epididymal phase of spermatogenesis, which leads to persistent azo- or oligospermia and morphological sperm abnormalities in male KTRs.	18
CMV infection	Reduced sperm quality.	19

References to studies in the right column.
ATG, anti-thymocyte globulin; AZA, azathioprine; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CS, corticosteroids; FSH, follicle-stimulating hormone; KTRs, kidney transplant recipients; LH, luteinizing hormone; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor.

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recipients (odds ratio 1.5), while preterm delivery, small for gestation age and congenital malformation prevalence was similar in post-transplant deliveries and the general population.[23] A major strength of this study was that the cohort included all consecutively transplanted males nationwide in Norway, as opposed to voluntary registry cohort studies subject to reporting bias. Unfortunately, the proportion of patients on MPA treatment was not given in this article. In a recent cohort study of children fathered by KTRs (n = 350, deliveries on MPA n = 155 and not on MPA treatment n = 195, Norway), Midtvedt et al[24] found no differences in congenital malformation prevalence or birth weight between the groups. A strength of this publication was the fact that the authors provided MPA trough-values close to the time of conception. Congenital malformations after maternal MPA exposure during pregnancy typically form a pattern of orofacial defects.[20] No such pattern was shown after paternal MPA exposure.[24] A recent small cohort study by Lopez-Lopez et al found a trend towards more miscarriages in pregnancies fathered by KTRs on MPA therapy (n = 20) compared with recipients not on MPA (n = 13, of whom 8 received azathioprine [AZA]) at the time of conception (18% versus 9%), but no difference in congenital malformations.[25]

Data accumulated from voluntary registries suggest that paternal exposure to corticosteroids (CS), calcineurin inhibitors (CNIs), cyclosporine A (CsA), tacrolimus (Tac), and AZA do not increase risk of obstetric complications or congenital malformations.[9] Data on pregnancies fathered by KTRs on mammalian target of rapamycin inhibitor (mTORi) or belatacept therapy are very limited. Antithymocyte globulin (ATG) or basiliximab are frequently used as induction therapy, and to the best of our knowledge, there are no data addressing the specific impact on male fertility or pregnancies fathered by KTRs receiving these drugs. Induction with rituximab can be used in ABO blood group incompatibility and in highly human leukocyte antigen (HLA)-sensitized patients.[26] A small meta-analysis of case reports by Mouyis et al[27] (n = 16) focused on pregnancy outcomes after paternal exposure to rituximab. From 9 pregnancies with reliable outcome data, there were 7 uncomplicated live births and 2 miscarriages, suggesting that paternal rituximab exposure is compatible with successful pregnancies, although paucity of data infer caution.[27]

PRE-CONCEPTION COUNSELLING IN FEMALE RECIPIENTS

Pregnancy and Graft Outcomes

Pregnancy is advisable beyond 1 year post-engraftment (Figure 1), when there has been no history of rejection during the last year, no current or recent fetotoxic infections, no or well-controlled hypertension, no or minimal proteinuria, stable graft function (serum creatinine <1.5 mg/dL, <133 µmol/L) and maintenance immunosuppression at stable dosing.[3] However, even then, pre-eclampsia, preterm delivery, low birth weight, and small for gestation age are prevalent in KTR pregnancies.[4-6] A 2-fold higher prevalence of gestational diabetes likely contributes to a higher risk of infections, some of which may be transmitted to the fetus. A 10-fold higher prevalence of hypertension in KTR pregnancies partly explains the high pre-eclampsia rate.[4] Nonetheless, KTR pregnancies on MPA-free regimens are not associated with a higher risk of miscarriage.[4-6] An increased risk of graft loss during pregnancy is shown for pregnancies during the first 3 years following transplantation, which in most cases were women with impaired renal graft function (serum creatinine >1.5 mg/dL/>133 µmol/L) at the time of conception.[4,28]

Adverse Maternal and Fetal Effects of Immunosuppressive Drugs

All immunosuppressive drugs commonly used after kidney transplantation cross the placenta to some degree, where they pass into the fetal circulation via the fetal intestine system and carry some risk of teratogenic and fetotoxic effects, and some also increase the risk of obstetric

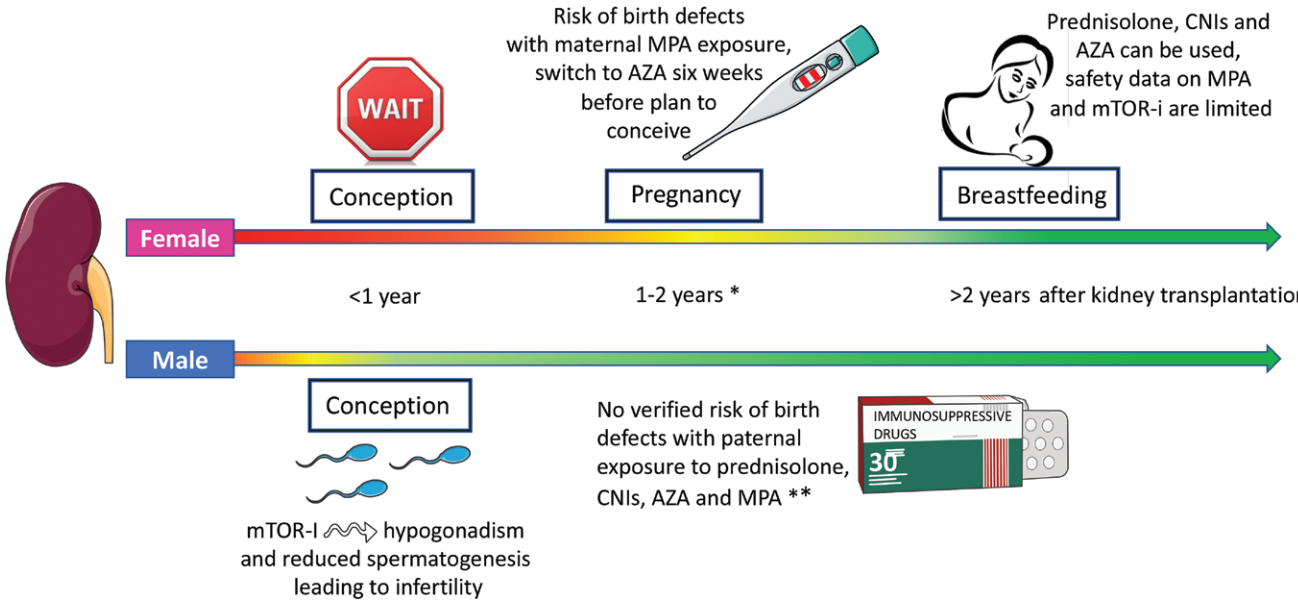

FIGURE 1. Immunosuppressive drugs and reproductive health after kidney transplantation. *Low-risk patient according to the American Society of Transplantation recommendation. **Prevalence of miscarriages is not known. AZA, azathioprine; CNI, calcineurin inhibitors; MPA, mycophenolic acid; mTOR-i, mammalian target of rapamycin inhibitor.

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TABLE 3.

Adverse effects on maternal, fetal and neonatal health from exposure to immunosuppressive drugs commonly used in kidney transplant recipients

	A. In utero drug exposure	
CS	CS pass freely across the placenta, where 90% is metabolized by placental 11-beta-hydroxysteroid dehydrogenase 2, converting prednisolone and methylprednisolone to inactive forms; hence, CS exposure in the fetal circulation is low.	29
CNI	About 70% of the maternal Tac dose crosses over to the fetus. The highly lipophilic nature of CsA allows it to diffuse passively across placenta and enter the fetal circulation, but the degree of transfer is uncertain, as fetal CsA concentration range from 37% to 64% of maternal CsA concentration.	30-32
MPA	MPA readily crosses the placenta and exert adverse fetal effects.	33
AZA	Maternal and fetal exposure appear to be similar, but unlike their mother, the fetus does not convert AZA from its inactive form to the active and possibly teratogen 6-mercaptopurine; hence, they are not subject to teratogenic or fetotoxic effects of AZA therapy.	34
mTORi	Very limited data.	
Belatacept	Very limited data.	
Basiliximab	Very limited data.	
Rituximab	Very limited data.	
ATG	Very limited data.	
	B. Maternal disease and obstetric complications	
CS	Adverse effects on glucose metabolism, hence increased risk of gestational diabetes.	1
CNI	CsA increases the risk of hypertension and dyslipidemia. Tac increases the risk of hyperglycemia. Both CNIs may impair renal function. Animal studies report intrauterine growth retardation with both CNIs and more preterm births after Tac exposure. In humans, the prevalence of obstetric complications in patients treated with Tac and CsA is similar to other immunosuppressive regimens, including preterm birth rate.	1, 33, 35
MPA	A multination European prospective study reported a relative risk of miscarriage of 45% after MPA exposure during pregnancy. Furthermore, prevalence of preterm birth was 62% and low birth weight 31% after MPA exposure.	36
AZA	Prevalence of obstetric complications after AZA therapy is similar to other MPA-free immunosuppressive regimens.	48
mTORi	Very limited data.	
Belatacept	Limited data. Two successful pregnancies on belatacept treatment have been reported.	33,37,48
Basiliximab	Very limited data.	
Rituximab	Limited data. A retrospective study of 153 non-transplant pregnancies on rituximab therapy, found a 22% miscarriage rate, 24% preterm births, 12% neonatal hematological abnormalities, two congenital malformations, one neonatal death, and one maternal death. Although there are reports of successful pregnancies on rituximab treatment, available data suggest that conception should be delayed after rituximab exposure.	33,38,48
ATG	Very limited data.	
	C. Congenital malformations	
CS	Animal studies report an increased risk of cleft palate with CS use. In humans, there are studies showing a higher prevalence of cleft palate, but most report no association, even at high doses.	39
CNI	Animal study showed skeletal retardation with CsA exposure. No increased prevalence or pattern of congenital malformations in humans.	40,41
MPA	MPA pose a major threat to the fetus with a congenital malformation prevalence of 26%. Structural malformations caused by MPA usually follow a specific pattern, with orofacial defects like microtia and cleft palate typically present. Other structural malformations reported are hypoplastic nails, short fifth finger, corpus callosum agenesis, myelomeningocele, hydronephrosis, atrial septal defect, and trachea-esophageal atresia. Rodent studies have shown a wide range of severe teratogenic effects as well as fetotoxic effects after MPA exposure, which might explain the high miscarriage rate.	20,36,42
AZA	Animal studies reporting congenital malformations probably do not apply to humans, where in utero exposure is low and there are only rare reports of congenital malformations. They include cases with hypospadias, polydactyly, hypogammaglobulinemia and atrial and ventricular septal defects, but there is no clear pattern of congenital malformations. Observational studies suggest that AZA is safe in pregnant women.	34,43
mTORi	Animal studies report a high risk of intra-uterine growth retardation, impaired skeletal ossification, and miscarriage after mTORi exposure. Safety studies on mTORi in pregnant women are scarce, with no congenital malformations reported.	44-46
Belatacept	Very limited data.	
Basiliximab	Very limited data.	
Rituximab	Very limited data.	47
ATG	Very limited data.	
	D. Infant drug exposure via breastmilk	
CS	Less than 0.1% of the maternal prednisolone dose is found in breastmilk, and even high doses of prednisolone and methylprednisolone were not associated with adverse neonatal outcomes.	71,72

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TABLE 3. (Continued)

	D. Infant drug exposure via breastmilk	
CNI	CNIs are excreted in breastmilk, but CNI absorption in the infant is limited. When maternal blood CsA concentrations were within the therapeutic range, CsA levels were undetectable in infant blood and only a transient reduction in infant lymphocyte number was shown. Similarly, infant serum Tac levels showed a constant rapid decline in lactating KTRs on Tac therapy, reflecting a shift from high in utero exposure to low postpartum exposure. Tac excretion into breastmilk was 0.2% of the maternal dose.	73-76
MPA	Limited data. MPA is highly protein-bound and therefore unlikely to be excreted in breastmilk in high concentrations. However, little human data exists on MPA treatment in lactating women; thus MPA cannot be recommended to lactating KTRs at present.	
AZA	The safety of AZA in lactating women is well documented, with only a small fraction of maternal AZA dose and 6-mercaptopurine detected in breastmilk. Long-term studies reported a prevalence of developmental abnormalities in children exposed to AZA through breastmilk at level with the general population.	77
mTORi	Very limited data.	
Belatacept	Very limited data.	
Basiliximab	Very limited data.	
Rituximab	Very limited data. Rituximab absorption from the infant gastrointestinal tract is likely very low due to its large molecular weight. However, due to lack of studies, lactating women who have recently been exposed to rituximab should abstain from breastfeeding.	
ATG	Very limited data.	

References to studies in the right column.
ATG, anti-thymocyte globulin; AZA, azathioprine; CNI, calcineurin inhibitor; CS, corticosteroids; CsA, cyclosporine A; KTR, kidney transplant recipients; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; Tac, tacrolimus.

complications and maternal disease,[1,20,29-48] presented in Table 3. MPA stand out with frequent birth defects with a typical pattern and a high miscarriage rate.[20] Other obstetric complications like preterm birth and intra-uterine growth retardation are also common after MPA exposure.[20] CS and CNIs put the pregnant recipient at increased risk of diabetes and hypertension.[1] Due to paucity of pregnancy outcome data on mTORi and belatacept, they are not considered the drug of choice in women who want to conceive and should be discontinued in case of pregnancy.[33,48] There is also very limited data on the impact of recent rituximab, basiliximab, and ATG exposure in pregnant women.[33,48] Some other drugs commonly used after kidney transplantation like statins, antiviral drugs, and angiotensin-converting enzyme inhibitors should also be discontinued in pregnancy.[3] In contrast, large amount of voluntary registry data accumulated over the last 6 decades suggest that CS, CNIs, and AZA can be used in pregnant KTRs with little risk of adverse effects on the fetus or graft.[3,48] Detailed discussions on this topic can be found elsewhere.[33,48]

Timing of Conception

The American Society of Transplantation recommends to avoid pregnancy during the first year after kidney transplantation and defer conception further in recipients at increased risk of fetal or maternal adverse events, including patients with diabetes, obesity, uncontrolled hypertension, moderate or severe proteinuria, advanced maternal age, multiple pregnancies, recurrent urinary tract infections, recurrent viral infections and/or use of antiviral agents, assisted fertilization, high-dose maintenance immunosuppressive therapy or immunosuppressive drug non-adherence.[3] Delaying conception implies that the recipient will miss valuable childbearing years and more patients will conceive at an advanced maternal age (≥35 y), which increases the risk of miscarriage,[4] or they may even miss their chance of conceiving. On the other hand, the prevalence of pre-eclampsia and preterm delivery was slightly higher in pregnancies conceived during the first 2 years after transplantation.[4] Some physicians have questioned whether the recommendation to defer conception beyond 1-year post-transplant could be further liberalized in selected recipients.[49] However, Gill et al[50] (n = 530 pregnancies, United States) reported a borderline increased risk of miscarriage in pregnancies during the first year after transplantation (odds ratio 1.7), suggesting caution. A recent study by Rose et al (n = 729 pregnancies, United States) showed an increased graft failure risk for pregnancies during the first 3 years post-engraftment,[28] suggesting that conception should be deferred in younger recipients.

Contraceptive Use and Interactions With Immunosuppressive Drugs

Typical use failure rates for available contraceptive methods and interactions between immunosuppressive and contraceptive drugs are presented in Table 4.[51–55] Long-acting reversible contraceptive methods like intra-uterine devices or progestin subdermal implants offer highly efficient contraception at level with sterilization, while failure rates are relatively high for contraceptive pills and barrier methods like condoms.[51] MPA and CS might interact with combined hormonal contraceptive drugs, reducing their efficacy.[56] An excellent review provides an in-depth discussion of safety and efficacy of available contraceptive methods in organ transplantation.[52]

Recent reports from Guazzelli et al (n = 197, Brazil) and Eide et al (n = 118, Norway) indicate that <10% of female KTRs of reproductive age use a long-acting reversible contraceptive methods,[57,58] even in the modern era where efficient contraception has received more focus.[8] It is disturbing that 51% of the Brazilian recipients and 37% of the Norwegian recipients could not recall having received any advice on contraceptive use from healthcare

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TABLE 4.

Contraceptive method efficacy and interactions with immunosuppressive drugs

Contraceptive method	Typical use failure rate (%)	Immunosuppressive drug interactions and transplant-related safety measures
Sterilization	0.5	No interaction. Female sterilization surgery might be complicated by previous abdominal surgery (kidney engraftment) and male partner sterilization or a long-acting reversible contraceptive method should be considered.
Progestin subdermal implant	0.05	Very limited safety data in KTRs.
Levonorgestrel IUD	0.2	Historically, KTRs received advice not to use IUDs due to anticipated reduced efficacy with concomitant use of immunosuppressive drugs and case reports of pelvic infections. These concerns have been refuted by later studies. It acts locally with no risk of drug interaction.
Copper IUD	0.8	No interaction. Can increase menstrual bleedings and should not be used in severe anemia or coagulopathy.
DMPA injection	6	No interaction. Increased risk of osteoporosis.
Progestin pill	9	Very limited safety data in KTRs.
CHC pill, patch or ring	9	Interaction with corticosteroids and mycophenolic acid-reducing efficacy. Increased risk of hypertension and venous thromboembolic disease.
Barrier method like condom or diaphragm	18	No interaction. Should only be used in combination with efficient contraceptive method and for protection against sexually transmitted diseases.

Table adapted from Krajewski CM, Geetha D, Gomez-Lobo V. Contraceptive options for women with a history of solid-organ transplantation. *Transplantation.* 2013;95:1183–6 and Trussell J. Contraceptive failure in the United States. *Contraception* 2011;83:397–404.
CHC, combined hormone contraception with estrogen and progestin; DMPA, depot medroxyprogesterone acetate; IUD, intrauterine device; KTR, kidney transplant recipient.

personnel.[57,58] Surprisingly, KTRs who received such advice used a barrier method more often than women who did not receive any contraception counseling.[57] Condom was the most frequent contraceptive method followed by contraceptive pills, and could partly explain the high rate of unintentional pregnancies.[57,58]

Shared Decision-making

Women of reproductive age who are scheduled for or have received a kidney transplant are faced with many dilemmas concerning reproductive health; hence, they need counseling. The treating physician must ensure that information about maternal, graft and fetal risks related to post-transplant pregnancy is comprehended by the patient. Recipients report a need for more information about reproductive health issues, and many feel that their physician does not support their wish to become pregnant.[59] Post-engraftment pregnancy rates have dropped after the introduction of MPA.[50] Some physicians might be reluctant to replace MPA with AZA due to a higher risk of rejection and therefore avoid pre-conception counseling or advice the recipient to avoid pregnancy.[60] To the best of our knowledge, physicians' attitudes toward pre-conception counseling in KTRs have not been studied.

Recipient autonomy may be lost, as their medical conditions complicate pregnancy decision-making. There are many aspects of reproductive and mental health that needs to be considered: Anxiety for congenital malformations and obstetric complications, pregnancy leading to impaired graft function and return to dialysis, guilt for disappointing their partner if they choose not to become pregnant or for becoming a mother with a somewhat reduced life-expectancy.[61] In addition to medical advice, physicians should offer the recipient psychological support and build their advice on the wishes, values, and acceptance of pregnancy-related risk to enhance patient autonomy and ensure shared decision making.[61] A recent Italian position statement on KTR pregnancies have incorporated shared decision-making in their recommendations to set a new standard in preconception counseling.[8]

Recipients with advanced maternal age and recipients who receive advice to delay conception for a minimum of 2 years after kidney transplantation may consider adoption. However, some transplant recipients experience restricted access to adoption services due to morbidity or shorter life-expectancy, leaving them no other chance for parenthood than pregnancy. It is critical that patients at particular high risk of adverse maternal or graft outcomes receive repeated personalized counseling on contraceptive use and timing of conception.[3,8]

Pregnancy management should be provided by a multidisciplinary team (nephrologist, a midwife and an obstetrician),[3] but there is at present little data to confirm that this service is actually provided.

Highly Human Leukocyte Antigen-Sensitized Patients

Highly HLA-sensitized KTRs have an increased risk of antibody-mediated rejection.[62] Pregnancy data on highly HLA-sensitized KTR pregnancies are very limited. Ajaimy et al[63] compared pregnancy and graft outcomes in sensitized (n = 8) and non-sensitized recipients. They found a higher cumulative incidence of pre-eclampsia, preterm delivery and low birth weight in sensitized patients, as well as a marked increase in antibody-mediated rejections leading to graft loss (n = 3 out of 8 sensitized recipients). These findings make clear that highly HLA-sensitized KTRs need to be explained the potential risk a pregnancy may pose for them, and physicians should ensure that they have understood this information. For the treating practitioner, it may seem clear that pregnancy is too risky and that they should consider not to proceed pregnancy due to a high risk for both the recipient and for the fetus. Nevertheless, some

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individuals may prioritize pregnancy so highly that they may be willing to take on this risk even after receiving balanced information from the medical team.

Assisted Fertilization

Successful pregnancy after assisted fertilization is possible after kidney transplantation, but data are limited to case-reports.[64] All studies reported healthy deliveries and no deterioration of graft function. However, 4 out of 5 cases were complicated by gestational hypertension, pre-eclampsia, premature rupture of membranes, and premature delivery.[64] In addition, assisted fertilization is associated with multiple pregnancies, which further increases the risk of obstetric complications.[65] These case reports do not include data specifically on the follicle-stimulating hormone pretreatment. Moreover, since only a few cases have been reported, there could be a publication bias underestimating adverse events after assisted fertilization in KTRs.[8]

MANAGEMENT OF PREGNANT AND LACTATING RECIPIENTS

Therapeutic Drug Monitoring

During pregnancy, cytochrome P450 3A4 is upregulated which increase CNI metabolism and reduce whole blood CNI concentrations.[31] In addition, plasma volume is increased and drug-binding red blood cell and albumin levels are lower, leading to a further decline in whole blood drug concentrations.[31] By the end of the first trimester, a 25%–50% increase in CNI dose could be necessary to maintain whole blood through levels. Adjusting the dose to reach target trough levels may, however, induce over-immunosuppression.[30]

Tac binds to red blood cell (85%–95%) and albumin (5%–15%), with only a minor unbound fraction. In line with Tac being a medium/low extraction drug, Zheng et al[31] showed that the unbound Tac concentration remained virtually unchanged, since the unbound clearance is only minorly increased, despite a 39% decline on average in whole blood trough levels during pregnancy. Moreover, no acute rejection episode was observed in 21 pregnancies in single kidney or simultaneous kidney-pancreas recipients, where Tac dosage was not adjusted despite lower whole blood trough levels.[66] The ideal Tac monitoring of pregnant KTRs would be measurement of the unbound Tac concentration. This is possible, but the technique is challenging and expensive and not commonly available.

Two Tac dosing strategies have been suggested: (1) maintain Tac dose unchanged from conception and throughout pregnancy, and only increase dose if whole blood through levels drop >50% or (2) adjust Tac dose to stay in the trough target range and decrease dose only if nephrotoxicity is suspected.[30] Until more robust data are available, we recommend to use strategy 2.

Most of circulating CsA is bound to red blood cell and plasma lipoproteins and the free fraction range between 4% and 12%.[67] Similar to Tac, CsA trough levels are based on whole blood measurements, but it is the free concentration that is active.[68] In a study on pregnant KTRs, CsA trough levels decreased on average by 23% in first trimester, 39% in second trimester, and 29% in third trimester compared with pre-conception levels.[68] The Transplant Pregnancy Registry International report that CsA dose was increased in 44% of KTR pregnancies, although dose adjustment is in theory not necessary.[69]

Acute Rejection Therapy

Pregnancy induce hyperfiltration and increased creatinine clearance, accompanied by a small reduction in serum creatinine level.[70] Thus, a small increase in serum creatinine is suggestive of an acute rejection episode, pre-eclampsia, CNI nephrotoxicity or in rare cases caused by the growing uterus obstructing flow through the transplant ureter.[2] To rule out ectopic pregnancies we recommend to perform a baseline ultrasound examination early after conception. In case of decreasing graft function during pregnancy, an indication ultrasound examination should be performed. If pre-eclampsia, urinary tract infection, and ureter obstruction are ruled out, an ultrasound-guided renal allograft biopsy can help establish the acute rejection diagnosis. With verified rejection, high-dose methylprednisolone therapy is considered safe in pregnant KTRs (Table 3), while there is insufficient safety data on ATG and rituximab to recommend their use in pregnant recipients.[3,48]

Unintentional Pregnancies

Data on the prevalence of unintentional KTR pregnancies are surprisingly scarce.[3] Some studies report that most KTR pregnancies were not planned,[58] in which use of contraceptive methods with high failure rates was reported in most cases. Maternal and fetal risks related to unintentional pregnancies in KTRs greatly exceed that of contraceptive use.[2] A major concern is MPA exposure during pregnancy, causing congenital malformations.[20] KTRs who have become unintentionally pregnant and express no clear intention to terminate the pregnancy, should without further delay, immediately replace MPA with AZA. There are no data on unintentional pregnancies on mTORi therapy; thus it should be discontinued and the immunosuppressive regimen changed to a combination of CS, CNI, and AZA. Repeated ultrasound examinations to look for signs of congenital malformations should be performed, but even severe structural malformations may not be visible in the early phase of pregnancy.

Breastfeeding

Recipients have traditionally been advised to refrain from breastfeeding to avoid transfer of immunosuppressive drugs to the infant via breastmilk.[71] In recent years, recommendations have been liberalized, since neonatal exposure to immunosuppressive drugs via breastmilk is extremely low[71-77] (Table 3). The recommended combination of CS, CNI, and AZA in pregnancy can be safely continued in lactating women.[71] Due to paucity of data, patients on MPA, mTORi or belatacept therapy, as well as patients recently exposed to rituximab are however recommended to avoid breastfeeding. When KTRs stop breastfeeding, patients who were switched from MPA to AZA before conception and have no plan for becoming pregnant again in the near future, should be converted back to MPA therapy to lower the risk of rejection. An excellent review provides an in-depth discussion of this topic.[71]

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TABLE 5.
Key points

Key points	Preconception counseling on timing of pregnancy and contraceptive use is essential to prevent unintentional pregnancies. It should be given before transplantation and repeated post-engraftment. The wishes, values, and acceptance of pregnancy-related risk of the recipient should receive attention.
	Assisted fertilization increases the risk of pre-eclampsia, but still result in live births.
	An immunosuppressive regimen consisting of CS, CNI, and AZA is considered safe in pregnant and lactating women.
	Whole blood CNI trough levels may be misleading in pregnant recipients.
	High-dose methylprednisolone can be used to treat acute rejections during pregnancy.
	Use of mTORi often precludes fertility in male recipients.
	The prevalence of congenital malformations in children fathered by recipients on MPA therapy at the time of conception was at level with the general population.

AZA, azathioprine; CNI, calcineurin inhibitor; CS, corticosteroids; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor.

CONCLUSIONS

This review mainly focuses on unresolved issues regarding immunosuppression and reproductive health in KTRs and point out some related key points (Table 5). There is a need for more knowledge on, for example, the impact of in utero exposure to mTORi and belatacept, CNI dosing strategies during pregnancy and possible effects of commonly used induction therapies like ATG or basiliximab. Additional studies on the impact of paternal MPA exposure on the fetus are also warranted. Pre-conception counseling is mandatory and should acknowledge the importance of recipient autonomy and shared decision-making.

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