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PREGNANCY AFTER KIDNEY TRANSPLANTATION: CLINICAL FEATURES, COMPLICATIONS AND OUTCOMES

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Pregnancy after kidney transplantation (KT) has become more common, but the risk of complications and adverse obstetric outcomes in this group of women remains high. **Objective:** to study pregnancy complications and outcomes in kidney recipients and renal graft (RG) survival after childbirth. **Material and methods.** The study included 22 pregnancies in 20 women with RG (transplants performed in 2006–2020). The comparison group consisted of 20 healthy women who had 20 pregnancies. Frequency and nature of pregnancy complications, neonatal health indicators, and pregnancy outcomes were evaluated. Graft survival was compared in the main group and in a group of 102 women after KT who did not have pregnancies. **Results.** Compared with healthy women, RG recipients had a higher rate of preeclampsia (25% and 0%, $p = 0.047$), fetal growth restriction (30% and 0%, $p = 0.020$), gestational diabetes (40% and 5%, $p = 0.020$), asymptomatic bacteriuria (35% and 5%, $p = 0.044$), preterm birth (60% and 0%, $p < 0.001$), and cesarean section (70% and 10%, $p < 0.001$). Median gestational age and birth weight were significantly lower in women with RG: 36.0 [33.9; 37.4] vs. 38.9 [38.9; 39.6] weeks, $p < 0.001$, and 2405 [2023; 2958] *vs.* 3355 [3200; 3690] g, $p < 0.001$, respectively. The rate of favorable pregnancy outcomes after KT was 81.8%, or 90% when early pregnancy loss is excluded. Two children were found to have genetic diseases passed from the mother. Graft survival did not differ between RG recipients with and without pregnancy, $p = 0.272$. **Conclusions.** Pregnancy outcomes in patients with RG are generally favorable, pregnancy and childbirth do not affect graft survival. When planning pregnancy after KT, it is necessary to consider the risk of complications and the possibility of transmitting genetic disorders to offspring.

Keywords: kidney transplantation, immunosuppression, pregnancy, complications, pregnancy outcomes, renal graft survival.

INTRODUCTION

Kidney transplantation (KT) provides the highest level of medical and social rehabilitation for patients with stage 5 chronic kidney disease (CKD); it enables many renal graft (RG) patients, both men and women, to exercise reproductive function [1, 2].

Although the pregnancy rate in this cohort is several times lower than in the general population, incidents of pregnancy among patients of kidney transplants are becoming regular occurrences [3, 4]. In recent years, assisted reproductive technologies, including *in vitro* fertilization programs, have even been used in post-KT patients suffering from infertility [5, 6]. Nevertheless, despite a fairly high rate of live births (>70% in most studies), pregnancy in RG recipients is associated with increased risk of complications and adverse outcomes. For instance, in a 2019 meta-analysis, which included 6,712 pregnancies in 4,174 kidney transplant recipients, the rate of spontaneous miscarriage was 15.4%, 95% CI 13.8–17.2, stillbirth was 5.1%, 95% CI 4.0–6.5, and preeclampsia was 21.5%; 95% CI 18.5–24.9 (for comparison, the population incidence of preeclampsia is 2–5%), pregnancy-induced hypertension was 24.1%, 95% CI 18.1–31.5, cesarean section was 62.6%, 95% CI 57.6–67.3, preterm delivery 43.1%, 95% CI 38.7–47.6 [7]. Adverse pregnancy outcomes and complications have been shown to be associated with reduced RG function before conception, especially when combined with severe proteinuria [8, 9].

A critical issue is the possible impact of pregnancy and childbirth on RG function and survival. Both individual studies and a large meta-analysis featuring 43 studies showed that pregnancy have no significant influence on kidney graft survival, although the rate of serum creatinine elevation was slightly higher in the first 2 years after delivery compared with women who did not have pregnancies after KT [10, 11].

The aim of our study is to investigate pregnancy complications and outcomes in kidney transplant recipients, as well as graft survival after delivery.

MATERIALS AND METHODS

Our longitudinal observational study included the main group – 20 kidney transplant recipients (among them one woman with a kidney and pancreas transplant)

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who had 22 pregnancies. The comparison group of pregnancy outcomes included 20 pregnancies in 20 healthy women; they did not differ from the post-KT pregnant women by age, body mass index, and number of pregnancies in medical history. A control group of 102 kidney recipients who had not become pregnant after KT and were comparable to the main group in terms of age, underlying disease (cause of end-stage chronic renal failure), and immunosuppressive therapy, was used to assess the effect of pregnancy and childbirth on renal graft survival.

Each pregnancy was treated as a separate case. Transplants were performed in 2006–2020 at different transplant centers. During pregnancy following KT, the patients were observed by a nephrologist and an obstetrician-gynecologist from the Moscow Regional Research Institute of Obstetrics and Gynecology.

All transplants were the first being performed on the patient. In 16 cases (80%), the KT was from a deceased donor (including kidney and pancreaticoduodenal complex transplantation), while 4 (20%) cases were transplantations from a living related donor. End-stage chronic renal failure was caused by the following: chronic glomerulonephritis (11 patients; 55%), congenital urinary anomalies (6; 30%), nephropathy of unknown origin (2 patients; 10%), and diabetic nephropathy resulting from type 1 diabetes (1; 5%). Mean age at the time of KT and at the time of delivery was 27.5 ± 6.7 years and 33.8 ± 5.5 years, respectively.

Twenty-one pregnancies were spontaneous, and one was achieved through *in vitro* fertilization. The first were 10 observed pregnancies, the second were 6, the third, fourth and fifth were 2 pregnancies each. At pregnancy onset, glomerular filtration rate (GFR) in the renal graft indicated stage 1 CKD in 5 (22.7%) cases, stage 2 in 9 cases (40.9%), stage 3 in 7 (31.8%), and stage 4 in a case (4.5%).

The patient with stage 4 CKD and creatinine level above 200 μmol/L before conception, according to Order 736 of the Ministry of Health and Social Development of the Russian Federation dated December 3, 2007, was indicated for early termination of pregnancy for medical reasons; however, the woman categorically insisted on prolonging the pregnancy and signed an official refusal to terminate it.

Another RG recipient, whose unplanned pregnancy occurred while taking teratogenic drug mycophenolate mofetil, was offered artificial abortion in the first trimester. She had a history of ischemic stroke with primary antiphospholipid syndrome, which sharply increased the risk of thrombotic complications during pregnancy. However, she also refused to terminate the pregnancy; the teratogenic drug was withdrawn in early gestation.

Artificial abortion at 20–21 weeks of gestation was offered to a woman whose second prenatal ultrasound screening revealed a serious fetal malformation – bilateral hydronephrosis with a high level of obstruction, suspected cystic dysplasia, and oligohydramnios, but the patient refused.

All pregnant women with a transplanted kidney were observed according to an individual protocol with the recommended frequency of visits to the doctor at least once every 2 weeks, self-monitoring of blood pressure (BP) and heart rate 4 times a day, monitoring of clinical blood count, daily proteinuria, serum creatinine at least once every 4 weeks in the first half of pregnancy and once every 14 days after the 20th week of gestation, urine microbiological examination at least once every 4 weeks, measuring tacrolimus/cyclosporine blood levels at least once every 2–3 weeks, kidney transplant ultrasound once every 6–8 weeks, fetal ultrasound with Doppler ultrasonography at least once every 4 weeks (more frequently if indicated) in the second half of pregnancy, determination of angiogenic coefficient sFlt-1/PlGF once every 4–5 weeks, use of global methods of assessing the hemostatic system – thromboelastography and thrombodynamics – if indicated. Daily blood pressure monitoring was done in addition to office standardized blood pressure measurements in case choosing antihypertensive therapy proved to be difficult. Current guidelines for the diagnosis of gestational diabetes mellitus (GDM) were followed [12].

In all patients after KT, mycophenolic acid medications were discontinued or replaced with azathioprine no later than 3 months before conception, considering their teratogenic and mutagenic effects, except for one case of unplanned pregnancy. ACE inhibitors, angiotensin receptor blockers, statins, urate-lowering medications (allopurinol, febuxostat), warfarin, direct oral anticoagulants, and other drugs that are prohibited for use during pregnancy were also discontinued at the planning stage.

During pregnancy, all RG recipients received corticosteroids in minimal doses (5–10 mg orally in terms of prednisolone) and a calcineurin inhibitor: tacrolimus was used in 17 (77.3%) cases, cyclosporine A in 5 out of 22 (22.7%). The third drug of the immunosuppressive therapy – azathioprine at a dose of 50 mg/day – was used in 12 out of 22 cases (54.5%). Any chronic hypertension was treated with drugs approved during pregnancy – methyldopa, dihydropyridine calcium channel blockers (long-acting nifedipine, amlodipine), selective beta-blockers (bisoprolol, nebivolol) – as monotherapy or in various combinations.

In patients with chronic hypertension, the target BP was considered 130/80–110/70 mmHg. All kidney recipients received folate, vitamin D (cholecalciferol), potassium iodide, and antiplatelet agents in pregnancy-recommended doses to prevent preeclampsia – acetylsalicylic acid 150 mg/day from the 13th to the 36th week of gestation (dipyridamole 225 mg/day in case of acetylsalicylic acid intolerance), and prophylactic doses of low-molecular-weight heparin throughout pregnancy

and 6–8 weeks postpartum to prevent thromboembolic and placenta-associated complications.

To treat anemia, oral or intravenous iron preparations were used; erythropoietin preparations were used in some cases of persistent anemia against the background of iron saturation and absence of folic acid and vitamin B_{12} deficiency.

The frequency and nature of pregnancy complications, neonatal health indicators, and pregnancy outcomes were assessed in women of both groups. An unfavorable outcome was considered to be artificial termination of a desired pregnancy early for medical reasons, antenatal, intranatal or postnatal fetal/newborn death, birth of a child with serious malformations or diseases leading to disability. A favorable obstetric outcome was defined as the birth of a live baby without significant developmental anomalies or hereditary diseases and the child's survival in the postpartum period.

Statistical data processing. Normally distributed values were presented as "mean ± standard deviation". Indicators with non-normal distribution were described as "median [first quartile; third quartile]"; qualitative indicators were presented in fractions (percent), or in absolute values. Indicators with distributions different from normal were compared using the Mann–Whitney U test for two independent samples. Fisher's exact test was used to assess the significance of differences in qualitative features (proportions in groups), and the Kaplan–Meier method was used to assess renal graft survival. The level of 0.05 was taken as the critical level of significance of differences.

RESULTS

The interval between child delivery and KT was quite significant – the median was 64.1 [49.5; 91.5] months, meaning that pregnancy occurred on average 5 years after transplantation. Compared to healthy women, pregnant women with transplanted kidneys had a significantly higher incidence of gestational complications, including preeclampsia, fetal growth restriction, GDM, anemia, and asymptomatic bacteriuria (ABU). Urinary tract infections were also more likely to occur (Table). Post-KT pregnancy had a higher incidence of both preterm birth in general (delivery before 37 weeks of gestation occurred in 60% of cases, 0% in the comparison group, $p < 0.001$) and delivery before 34 weeks of gestation (25% in the main group and 0% in the healthy group, $p = 0.047$). The reasons for premature birth were preeclampsia in 4 (33.3%) cases, signs of fetal distress (decompensated fetoplacental insufficiency) in 3 (25%), onset of labor in 2 (16.7%), prenatal amniotic fluid discharge in 1 (8.3%), progressive increase of proteinuria in 1 case, and reversible increase of serum creatinine in 1 case.

Patients with kidney transplants had significantly higher rates of surgical deliveries than healthy patients: the main group had 70% of caesarean sections, whereas the control group had 10%, or seven times less, $p < 0.001$.

Median delivery time, median absolute birth weight and percentile birth weight were significantly lower in the transplanted kidney group. Additionally, the children born required treatment in the intensive care unit more often.

There were no rejection crises or kidney graft losses during pregnancy. In addition to active urinary infection (which every fifth pregnant woman with a transplanted kidney had during pregnancy) and ABU, other infections

Table

Pregnancy complications and obstetric outcomes in women with a transplanted kidney and in healthy women

Indicator	Women after KT	Healthy women	p
Incidence of preeclampsia	5 (25%)	0 (0%)	0.047
Incidence of intrauterine growth restriction	6 (30%)	0 (0%)	0.020
Incidence of gestational diabetes mellitus	8 (40%)	1 (5%)	0.020
Incidence of anemia	17 (85%)	7 (35%)	0.003
Incidence of asymptomatic bacteriuria	7 (35%)	1 (5%)	0.044
Incidence of active urinary tract infection	4 (20%)	0 (0%)	0.106
Proportion of births before 37 weeks of gestation	12 (60%)	0 (0%)	<0.001
Proportion of births before 34 weeks of gestation	5 (25%)	0 (0%)	0.047
Rate of cesarean section	14 (70%)	2 (10%)	<0.001
Due date (weeks)*	36.0 [33.9; 37.4]	38.9 [38.9; 39.6]	<0.001
Children's body weight at birth (g)*	2405 [2023; 2958]	3355 [3200; 3690]	<0.001
Children's body weight at birth)%)*	45 [23; 58]	61 [42; 77]	0.045
Rate of newborn transfer to the ICU	9 (45%)	0 (0%)	0.001
Favorable pregnancy outcome**	18 (81.8%)	20 (100%)	0.109

Note: *, indicator is presented as median [Q1; Q3]; **, indicator is calculated for 22 cases (all pregnancies that occurred), all other indicators are calculated for 20 pregnancies that ended in childbirth.

were observed in this group during gestation: herpes simplex in 1 case, shingles, bacterial tonsillitis, acute bronchitis, and food poisoning in 1 case each. Two patients had mild COVID-19 during pregnancy, and one had asymptomatic COVID-19 infection (tested positive to nasopharyngeal swab test). The virus was detected to have replicative activity during pregnancy in one recipient with chronic hepatitis B infection; a hepatologist prescribed antiviral therapy – tenofovir alafenamide 25 mg/day – for the entire gestational period. In all, 11 out of 20 (55%) pregnancies that ended in childbirth had infectious complications.

Out of 22 pregnancies, 20 (90.9%) ended in childbirth, there were 2 (9.1%) cases of first trimester nondeveloping pregnancy. Live birth rate was 90.9%. One newborn girl with prenatally diagnosed serious urinary anomalies (parents refused to terminate pregnancy) and congenital renal failure died on day 3 of birth despite renal replacement therapy by peritoneal dialysis. The cause of death was pulmonary dysplasia. Another child (a girl) inherited from her mother a genetic disease – oral-facial-digital syndrome type I with an X-linked dominant inheritance – while no internal organ abnormalities were detected in the girl; the early adaptation period was generally favorable. Thus, despite the child surviving in the latter case, the pregnancy was classified as an unfavorable outcome; favorable outcomes were observed in 18 out of 22 (81.8%) pregnancies. If we do not take into account early pregnancy loss (before 13 weeks), which often occurs in the general population, the rate of favorable outcomes is 90% (18 out of 20 pregnancies that reached 20 weeks). Children born to mothers with a transplanted kidney grow and develop normally.

Separately, we studied the renal graft status at the current time point (December 2023) in patients who had a pregnancy and delivery (Fig. 1). Median follow-up time after delivery was 26.9 [13.2; 47.1] months. The majority (72.8%) of women continued to be followed up with a functioning RG, 18.2% of recipients left follow-up. One patient (4.5%) lost the graft and returned for dialysis 4 years after delivery, which resulted in a second unplanned pregnancy that became complicated by preeclampsia. One patient with a history of primary antiphospholipid syndrome and two strokes died with a functioning graft from a recurrent stroke 20 months after delivery with a favorable obstetric outcome.

We analyzed RG survival after delivery (Fig. 2). One-year graft survival rate after delivery was 100%, 2-year survival was 92.3%, and 5-year survival was 73.8%.

To evaluate the effect of pregnancy and delivery on RG survival (from the time of transplantation), we compared graft survival in the main group and in the control group (women with a transplanted kidney who had no pregnancies after KT) (Fig. 3).

It turned out that there was no significant difference in RG survival rate between the main and control groups, $p = 0.272$.

DISCUSSION

The rate of favorable pregnancy outcomes was high – 81.8% or 90% (when early losses are taken out of the picture). These rates are comparable with those arrived at by other researchers [1, 7, 8, 13], even though some of our patients were contraindicated to carry a pregnancy to term but refused to terminate it. The rates of preeclampsia, intrauterine growth restriction, preterm labor, and operative delivery were higher than in the general population, which is consistent with reports [7, 14, 15]. At the same time, average delivery time (36 [2023; 2958] weeks) and birth weight (2405 [2023; 2958] g) provided a favorable prognosis in most cases for newborn nursing.

The high incidence of GDM in our cohort of pregnant women – 40% – is noteworthy, which is higher than the 2–6% rate described in other studies on pregnancy complications after KT [7, 16]. Apparently, this difference is because we paid special attention to this pregnancy complication, taking into account the adverse effect of hyperglycemia on gestational outcomes, and we used modern diagnostic criteria, which may have contributed to improved GDM detection [12]. In all cases, it was early GDM, largely associated with the diabetogenic effect of immunosuppressive drugs – calcineurin inhibitors and corticosteroids.

Prevention and treatment of infectious complications play a significant role in achieving favorable pregnancy outcomes after KT. Incidence of these complications in

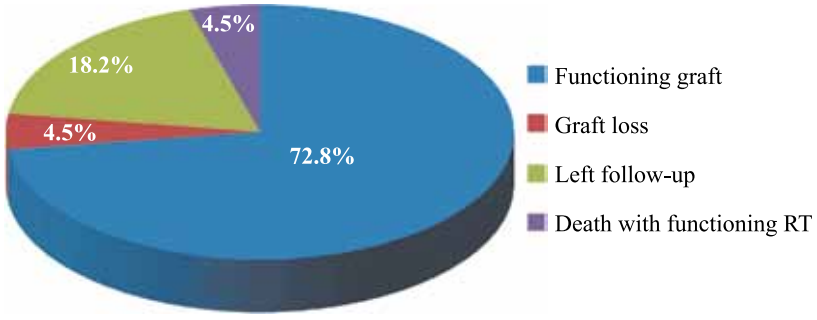

Fig. 1. Renal graft status after delivery

the pregnant women was quite high, 55%, but there were no severe infections. Urinary tract infection was the most common – in 7 out of 20 cases (35%) – and 4 pregnant women (20%) had both ABU and active infection. Active antibiotic treatment of all ABU episodes may have been important in preventing severe urinary infection.

In our study, there were no cases of acute graft rejection during pregnancy. This is probably due to the small size of our cohort. In a meta-analysis, the rate of rejection in pregnancy among 822 RG recipients was 9.4% (95% CI 6.4–13.7), which was comparable to the rate of rejection outside of pregnancy [7, 17]. Apparently, acute RG rejection is not a frequent pregnancy complication, especially with careful pharmacokinetic control and timely adjustment of immunosuppression, although the risk of rejection is still not zero, especially in the first 2–3 years after delivery.

It should be noted that most of the unfavorable outcomes occurred in unplanned pregnancies, when pregnancy was either contraindicated at all, or there were no clear contraindications but no pregravid preparation was carried out. A special problem is the possibility of the child inheriting a genetic disease from the mother. A patient with proven oral-facial-digital syndrome type I with an X-linked dominant inheritance and polycystic kidney disease, 50% risk of transmission regardless of sex, absolute mortality for male fetuses, was recommended (by a consilium with the participation of a geneticist) to get pregnant via IVF followed by preimplantation genetic testing in order to select female embryos with a favorable prognosis for the disease. However, the patient did not agree with the proposed tactics and became spontaneously pregnant, which resulted in transmission of the disease to the child. However, since the sex of the fetus

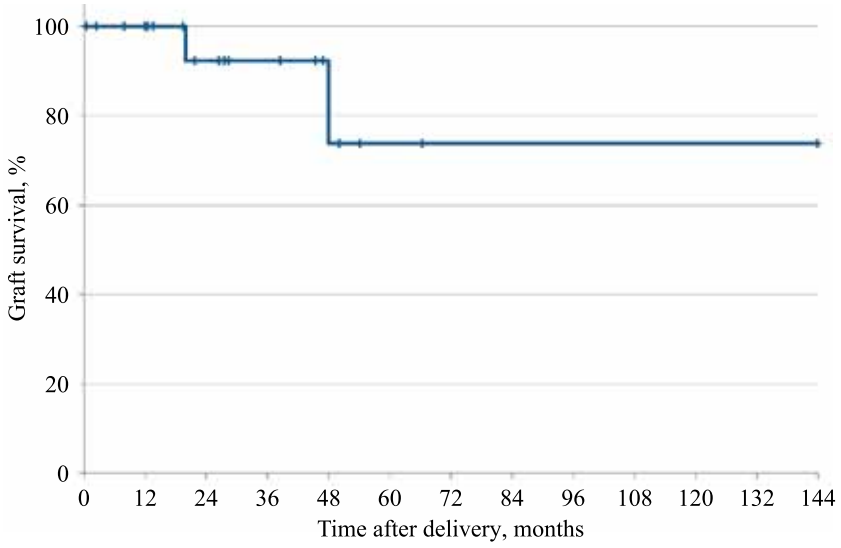

Fig. 2. Kidney graft survival after delivery

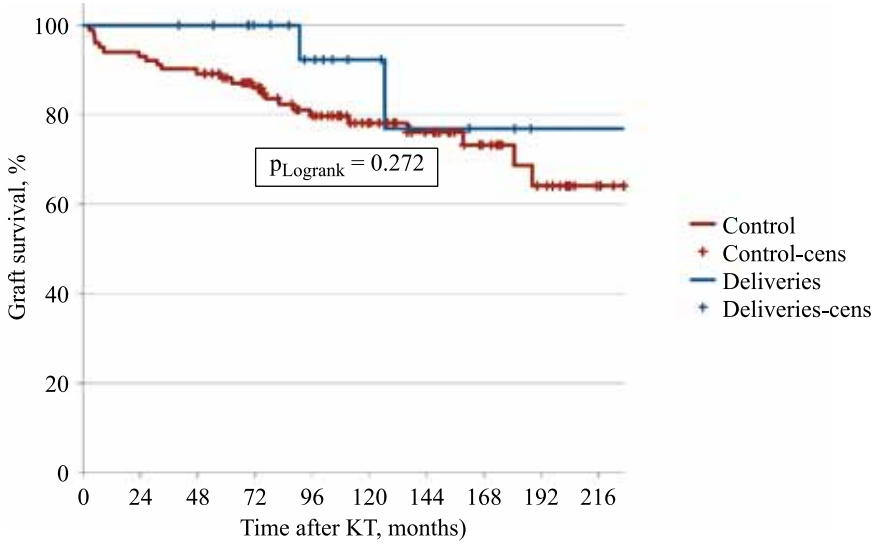

Fig. 3. Kidney graft survival (from the time of surgery) in women with and without pregnancy after transplantation

was female, there was no immediate threat to life during intrauterine development and in the neonatal period.

Another patient, who had not undergone pregravid preparation and came for a hospital appointment for the first time with pregnancy, was diagnosed with a urinary tract anomaly – neuromuscular dysplasia of both ureters, right-sided ureterohydronephrosis, and hypoplasia of the left kidney; the disease was not suspected to be hereditary in nature. The first fatal ultrasound screening detected no abnormalities, but at 20 weeks, the fetus was found to have a defect – bilateral hydronephrosis, high level of obstruction, suspected cystic renal dysplasia, and oligohydramnios. The parents refused to terminate the pregnancy and, unfortunately, the perinatal outcome was unfavorable. We cannot exclude the hereditary nature of the disease in this case, so the patient should undergo exome sequencing if she is planning a second pregnancy. In patients with CAKUT (congenital anomalies of the kidneys and urinary tracts) syndrome with bilateral lesions, monogenic anomalies can be detected in 22% of cases [18]. Thus, despite the relatively low frequency of hereditary diseases among pregnant women with RG, it is necessary to keep in mind the possible transmission of diseases to children and the advantages of using (in the presence of established mutations) modern assisted reproductive technologies.

When comparing graft survival in patients who carried a pregnancy and those who did not have pregnancies after KT, comparable in age, underlying disease, and nature of immunosuppression, no statistically significant differences were found; this does not contradict the finding from other researchers [10, 11]. However, given that pregnancy is usually allowed in patients with initially satisfactory RG function and without serious immunologic or non-immunologic complications, this comparison may not be entirely valid. To some extent, these 'advantages', when analyzing outcomes, may be offset by cases where pregnancies are unplanned in patients with non-ideal RG function or other contraindications to fertility and the woman insists on prolonging the pregnancy. Once again, we emphasize that in kidney transplant recipients, lack of pregnancy planning and pregravid preparation can have a negative impact on obstetric and nephrological outcomes.

CONCLUSION

Pregnancies can succeed in women who are kidney transplant recipients if there is careful selection of genetically healthy embryos, pregravid preparation and personalized management, despite their higher incidence of pregnancy complications compared to healthy women. When planning pregnancy after KT, one should keep in mind the possibility of transmitting hereditary diseases to the offspring: where there are no contraindications, IVF with preimplantation genetic testing and selection of genetically healthy embryos can be performed. Pregnancy after KT does not appear to have a significant effect on long-term graft survival, although further research on this is needed.

The authors declare no conflict of interest.

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