НИРКИ KIDNEYS

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Pregnancy after kidney transplantation: effect on maternal and foetal health

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Abstract. ***Background.*** *Pregnancy in kidney transplant recipients is high-risk due to immunosuppression, pre-existing comorbidities, and graft function concerns. Optimal maternal and foetal outcomes require a multidisciplinary approach and favourable baseline conditions. Objective: to identify ideal conditions for pregnancy in kidney transplant recipients and evaluate the impact of pregnancy on maternal and graft outcomes.* ***Materials and methods.*** *It was the retrospective observational study conducted at the Department of Obstetrics and Gynaecology of the Institute of Kidney Diseases and Research Centre (Ahmedabad, India) from 2014 to November 2020. A total of 27 pregnancies in kidney transplant recipients were analysed. Maternal nephrological parameters, obstetric complications, and graft function were assessed during and after pregnancy. Key outcomes measured included time between renal transplantation and conception, live birth rate, maternal renal function, and neonatal health. Data were collected from clinical records and analysed retrospectively.* ***Results.*** *The primary outcomes were the interval between renal transplantation and conception, live birth rate, and maternal renal function pre- and post-pregnancy. The mean age at transplantation was 28.70 ± 3.82 years, and the mean age at conception was 31.07 ± 2.57 years. The average time between transplantation and conception was 47 months. Median serum creatinine was 1.13 ± 0.39 mg/dL at conception and 1.09 ± 0.45 mg/dL postpartum. Sixteen pregnancies (59 %) resulted in live births. Common complications included preeclampsia (6 cases, 22.22 %), preterm delivery (16 cases, 59 %), and low birth weight (9 cases, 33.33 %). Caesarean section was performed in 14 patients (52 %).* ***Conclusions.*** *Pregnancy in kidney transplant recipients is feasible under strict monitoring and does not significantly affect graft function when optimal conditions are met. Outcomes are influenced by adequate pre-pregnancy renal function, stable immunosuppressive therapy, and multidisciplinary care.*

Keywords: *post-kidney transplant pregnancy; high-risk pregnancy*

Introduction

Renal transplantation is certainly life-saving in the lives of patients suffering from renal failure. It improves the quality of life and is helpful for those who want to conceive. Fertility declines because of a decline in sexual drive and gonadal dysfunction in patients with progressing kidney diseases. In certain conditions, pregnancy in patients with kidney grafts is conceivable [1]. However, pregnancies with these specific conditions are considered high risk especially because of the inevitable treatment of immunosuppressive drugs, underlying kidney disease and other comorbidities. Statistics from the United Kingdom national cohort, propose that most renal transplant recipients can achieve successful pregnancies, although adverse events are common [2]. Among females after renal transplantation the risk of pregnancy-related complications, including preeclampsia/gestational diabetes, caesarean section, prematurity, foetal growth restriction and low birth weight compared to the general population are significantly higher in these patients [3]. It was recently revealed in a cohort of 56 female transplant recipients that adequate graft function (creatinine < 110 μmol/l) was positively correlated with pregnancy-related complications such as preeclampsia and preterm delivery [3]. Preterm delivery is related to several acute and chronic complications including respiratory distress syndrome, intracranial haemorrhage, apnoea, retinopathy of prematurity, seizures, necrotizing

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enterocolitis and temperature instability [4]. These infants are at high risk of long-term neurodevelopmental morbidities such as cerebral palsy, mental disorders and impaired learning [4]. Data on children's initial longitudinal development in pregnancies after kidney transplantation are rare even though many reports on successful pregnancies in kidney transplant recipients are available [3, 4]. Data suggest that these children's cognitive development is no different from that of controls [5]. An earlier National Transplant Pregnancy Registry analysis of children exposed in utero to cyclosporine, revealed no increased risk of birth defects, significant problems with renal function, attention-deficit hyperactivity disorder or neurocognitive or immune development [6]. These findings are in sync with results from previous studies that show a good rate of sufficiently developed children born to kidney-transplanted mothers [6]. According to a recent report, corticosteroids, cyclosporine, tacrolimus and azathioprine are, in general, safe drugs during pregnancy in renal transplant recipients [7].

The purpose of this retrospective study was to assess pregnancies following kidney transplantation and their impact on mother, graft and foetus/early childhood with longitudinal observation up to 2 years after delivery.

Materials and methods

This was an observational retrospective, single-centre study. The study design was reviewed and approved by the local Ethics Committee. Entitled patients were all renal transplant recipients who became pregnant between 2014 and 2020. Subsequently, all transplant recipients retain their follow-up in the same institution throughout their lives after transplantation, and all tests are performed in a single central laboratory, patients who were getting pregnant spontaneously or were trying to conceive through Artificial reproductive techniques were actively selected. The main outcome was the occurrence of any maternal complication. Information regarding the preconception period (3 to 12 months before conception), each trimester of the pregnancy and short-term follow-up (12 months after delivery) was collected from the medical records maintained by the institution. For this analysis, each pregnancy was considered an event. Clinical and laboratory parameters were described. During antenatal follow-up, these patients were advised to visit every month till 20 weeks and thereafter every 15 days till 28 weeks and thereafter weekly follow-up. All women received continuous haematinics during pregnancy and follow-up. Urine samples were collected for culture in each medical visit, and all bacteriuria, even asymptomatic, was treated appropriately. Proteinuria was evaluated in isolated urine samples, and the result was expressed as g/L. Preeclampsia was defined according to NICE guidelines for hypertension in pregnancy. Renal function (serum creatinine) and proteinuria over time were assessed by repeated measures analysis method. Children were followed up in paediatric OPD till 2 years of age for any developmental delay.

Statistical analysis

All collected data were entered into the SPSS V20 and analysis was conducted. Quantitative variables were expressed as mean and standard deviation. Non-continuous data were countable and were expressed as percentages or numbers. Fisher exact test was used for comparing groups. P-value. P-value < 0.05 was considered to be statistically significant. NS represents a non-significant difference between groups.

Results

The mean age at the time of renal transplantation was 28.70 years (32.40 ± 3.82). The average age at the time of conception is 31.07 ± 2.57 years. The average time between renal transplantation and the occurrence of pregnancy was 3.97 ± 2.14 years. Of the 27 pregnancies, 16 (59 %) resulted in the birth of a living child. Toxaemia was found in 6 (22.22 %) cases, low birth weight in 9 (33 %), preterm in 16 (59 %) and intrauterine growth retardation in 1 (3.70 %). Caesarean section was indicated in 14 (52 %) cases. The most common cause of renal transplant was crescentic glomerulonephritis (59 %) followed by other causes (Fig. 1).

There were five patients who had past history of gestational hypertension and 4 patients who had a past history of preeclampsia, which might have led to acute renal and chronic renal failure (in 10 patients) necessitating renal transplant for survival. The reason for these patients landing up for renal transplant might be inappropriate control of blood pressure and poor compliance in taking antihypertensive drugs in the postpartum period. The mean transplant pregnancy interval was 47 months. Pregnancy outcome con-

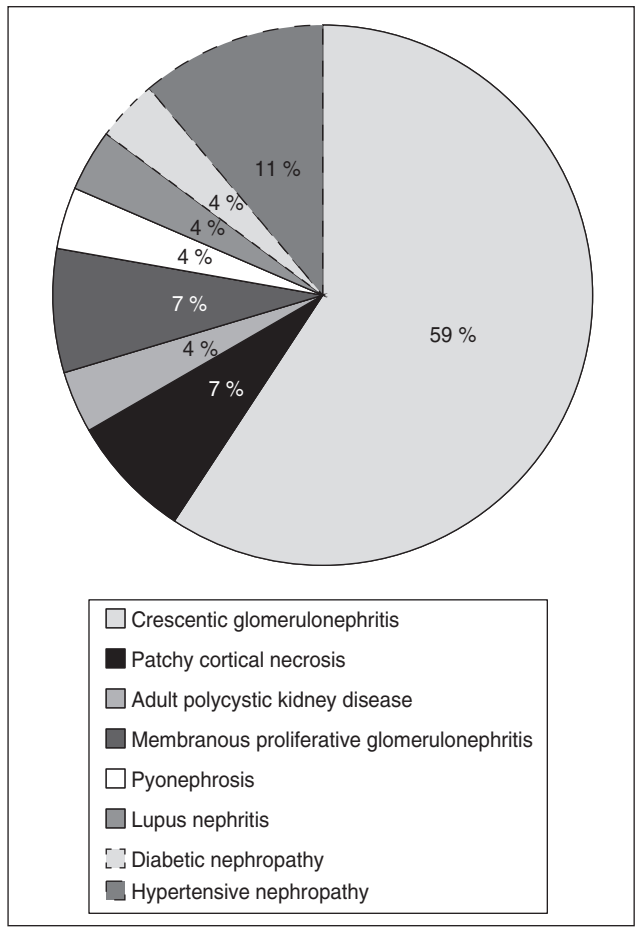

Figure 1. Causes of renal transplant

cerning transplant pregnancy interval was studied (Table 1). It was found that patients with transplant pregnancy interval > 2 years had good outcomes, where out of 27 patients, 16 patients had delivered successfully with healthy babies, except one who had early preterm delivery at 28 weeks.

The effect of serum creatinine pre-pregnancy and during the antenatal period on pregnancy outcome was studied (Table 2). The mean pre-pregnancy serum creatinine level was 1.14 ± 0.39 mg/dl. The number of deliveries was higher in patients with pre-pregnancy serum creatinine < 1.2 mg/dl. For patients with serum creatinine at around 1 mg/dl, one had preterm delivery at 28 weeks and 16 patients had term delivery.

All routine antenatal investigations like complete blood counts, blood urea nitrogen, and urine routine examinations were within normal limits, apart from 1 patient whose haemoglobin was 8.8 gm/dl and 2 patients who had pus cells and proteinuria in urine routine micro examinations. No gross anomaly was detected in a foetus during an antenatal scan. Graft Doppler was also normal in all antenatal patients.

Among antenatal complications, one patient had cholestasis of pregnancy from 7 months of gestation, which was managed conservatively. 17 patients were chronic hypertensive, out of which, 8 patients had missed abortion, 6 patients had term delivery who remained mild hypertensive throughout pregnancy and one developed preeclampsia superimposed on chronic hypertension around 34 weeks of gestation. Three patients developed newly diagnosed gestational hypertension from 20 weeks of gestation, out of which 2 patients developed preeclampsia at 32 weeks. Both preeclamptic patients were delivered around 36 weeks by caesarean section along with steroid coverage for the foetus and delivered healthy babies.

The effect of various immunosuppressive agents on pregnancy outcomes was also studied (Table 3). Out of 27

Table 1. Pregnancy outcome with respect to transplant pregnancy interval

Pregnancy outcome	Transplant pregnancy interval		P-value
	< 2 years (N = 9)	> 2 years (N = 18)	
Abortion	5 (55.56 %)	2 (11.11 %)	0.02 (S)
Delivery	4 (44.46 %)	16 (88.89 %)	

Table 2. Effect of serum creatinine levels on pregnancy outcome

	Serum creatinine	Abortion (N = 6)	Delivery (N = 21)	P-value
Pre-pregnancy	≤ 1.2 mg/dl	3 (50 %)	16 (59 %)	0.32 (NS)
	≥ 1.2 mg/dl	3 (50 %)	5 (41 %)	
		Abortion (N = 4)	**Abortion (N = 23)**	
Pregnancy	≤ 1 mg/dl	1 (25 %)	15 (55 %)	0.27 (NS)
	≥ 1 mg/dl	3 (75 %)	8 (45 %)	

Table 3. Immunosuppressive agents and pregnancy outcome

Immunosuppressive agents, n (%)	Antenatal complications, n	Foetal complications, n	Postpartum complications, n
Prednisolone — 5 (18.5)	Missed abortion — 3		
Prednisolone + cyclosporine — 2 (7.4)	Missed abortion — 1 Chronic hypertension — 1		
Prednisolone + azathioprine — 1 (3.7)	Cholestasis of pregnancy — 1	IUGR — 1	
Prednisolone + tacrolimus — 6 (22.2)	Missed abortion — 2 Chronic hypertension — 5 Preeclampsia superimposed on chronic hypertension — 1	Cardiac anomaly (VSD) — 1[a]	
Prednisolone + cyclosporine + azathioprine — 6 (22.2)			Delayed LSCS wound healing — 1 Bells' palsy — 1
Prednisolone + azathioprine + tacrolimus — 7 (25.9)	Gestational hypertension + PROM (at 34 weeks) — 1 Missed abortion — 1		

Notes: [a] — the use of tacrolimus therapy during pregnancy is not associated with increased risk of congenital malformations. Cardiac anomaly might be sporadic in occurrence.

pregnant patients, 4 had preterm deliveries. One patient delivered at around 28 weeks and 3 patients at 34 weeks of gestation. 1 preterm delivery was due to PROM and 2 preterm was due to preeclampsia and 1 was due to IUGR. All of them had caesarean delivery except one who had preterm vaginal delivery at 28 weeks. The mean weight of babies was 2.38 ± 0.54 kg and the mean maturity was 35.53 ± 2.33 weeks (Table 4). Out of 16 babies, one expired due to cardiac anomaly (VSD) which was during postpartum day 3, one baby was in neonatal intensive care for 30 days because of prematurity and low bright weight (1 kg at 28 weeks), and another for preterm. The rest 13 babies were normal. During postpartum follow-up, one patient had acute graft rejection 2 months after abortion which was managed conservatively. One patient suffered from Bell's palsy in the postpartum period which was managed conservatively, and another patient was infected with COVID-19 at 4 months of pregnancy and was referred to another hospital which had facilities to treat pregnant patients with COVID-19. Maternal estimated glomerular filtration rate (eGFR) and neonatal creatinine values are shown in Table 5.

Discussion

Managing kidney transplant receivers begins from their peri-transplant period. The peri-transplant psychoanalysis is important for these patients to realize the effect of pregnancy on grafted kidneys and guidance related to the proper period to conceive. A recent meta-analysis concluded that pregnancy in these populations is associated with high chances of maternal and foetal complications hence necessitating holistic counselling and management [8].

According to the American Society of Transplantation Consensus Opinion, as long as graft function is good, the patient can conceive. Graft function is considered to be optimum when serum creatinine < 1.2 mg/dl, with < 500 mg/24 h protein excretion. However, when the interval between kidney transplant and pregnancy is more than 5 years, it may cause impairment of renal function, due to reduced tolerance of grafted kidney to physiology of pregnancy but with suitable supervision and follow-up these can be prevented. In this study, patients with transplant pregnancy interval greater than 2 years had good pregnancy outcomes with 15 full-term and 1 preterm delivery.

During the antenatal period, these patients are at risk of developing hypertension, as a result of either pre-existing chronic hypertension or gestational hypertension, which needs to be managed aggressively [9]. In our study, out of 27 patients, 17 patients were chronically hypertensive, and 3 patients had gestational hypertension. Out of 17 chronic hypertensive patients, 8 had abortions, 6 were mild hypertensive throughout the pregnancy and 1 patient had preeclampsia superimposed on chronic hypertension. Gestational hypertension and mild chronic hypertension were managed with methyl dopa, which is still preferred for mild hypertension as it is well tolerated and does not cause uteroplacental insufficiency [9]. Other antihypertensive agents like labetalol, nifedipine, and thiazide diuretics

Table 4. Characteristics of newborns

Live births	N = 16 (%)
Mean gestational age	35.53 ± 2.33 weeks
Extreme preterm (< 28 weeks)	0
Very premature birth (28–32 weeks)	1 (6.25 %)
Moderate to late premature birth (32–37 weeks)	15 (93.75 %)
Term (> 37 weeks)	0
Median birth weight	2303.00 ± 0.52 g
Small for gestational age	1 (6.25 %)
Adequate for gestational age	15 (93.75 %)
3000–3500 g at birth	0
2500–3000 g at birth	8 (50 %)
< 2500 g, low birth weight	8 (50 %)

Table 5. Maternal eGFR and neonatal creatinine values

Parameter	Mean ± SD	Range	Time point	Additional notes
Maternal eGFR at conception	65.2 ± 12.3 mL/min/1.73 m^2	48.0–89.0	At conception	Indicates baseline renal function
Maternal eGFR postpartum	66.8 ± 11.7 mL/min/1.73 m^2	50.0–90.5	6 weeks postpartum	Shows renal recovery post-pregnancy
Neonatal creatinine	0.85 ± 0.12 mg/dL	0.6–1.1	First 48 hours of life	May reflect maternal creatinine levels

can be used depending on the grade of hypertension [9, 11]. These patients can develop superimposed preeclampsia which causes grave maternal and foetal complications, like renal failure, liver failure, HELLP syndrome (haemolysis, elevated liver enzymes, and thrombocytopenia), eclampsia, stroke and even maternal mortality. In a foetus, it can result in small for gestational age, preterm delivery, hypoxic injury, and foetal loss [10]. It is problematic to diagnose preeclampsia early in kidney recipients as they already have proteinuria and blood pressure usually buds in the third trimester of pregnancy.

There is the likelihood of graft rejection throughout pregnancy, but it is hard to diagnose with variations in serum creatinine. Whenever altered graft function is detected on Doppler, it is significant to exclude graft rejection secondary to preeclampsia and other renal causes. If supposed, a biopsy of the kidney should be done under the guidance of ultrasonography [11]. There is inadequate evidence for the use of muromonab-CD3 or anti-thymocyte globulin for treating graft rejection. It can be conservatively treated alone with corticosteroids [11]. In this study too, 1 patient had acute graft rejection 2 months after abortion was managed with plasmapheresis and steroids. American Society of Transplantation Consensus Conference recommends that in order to reduce the incidence of graft rejection, a dose of immunosuppressant drugs must be sustained at pre-pregnancy levels throughout pregnancy. Hence, the serum level of these drugs needs to be checked during the antenatal period [12]. In our study, the levels of immunosuppressant drugs were monitored. Further antenatal complications like gestational diabetes, anaemia, and infections such as urinary tract infections can occur [13]. These patients are susceptible to advanced infections like toxoplasmosis and infection with herpes simplex virus, HIV, varicella zoster, hepatitis B or C virus [14]. Antenatal diagnosis should be done to detect these infections and patients should be vaccinated with live vaccines like rubella before transplant. In the majority of cases, caesarean section is the favourable route of delivery however normal vaginal delivery can be directed uneventfully.

Other than these stated risks, kidney transplant recipients are also at higher risk for PROM, which can progress to higher chances of preterm delivery and low birth weight children [11]. So, it is highly recommended to give corticosteroids later in pregnancy (between 28 and 34 weeks) to help in foetal lung maturity [11, 13]. The incidence rate of foetal intrauterine growth restriction is 25–55 %, due to adverse effects of already existing hypertension and renal disease [15]. So, alongside with patient, it is vital to carefully check for foetal growth to diagnose foetal growth restriction as early as possible [11].

Preterm offspring, even if born in late preterm (34–36 gestational weeks) are at an increased risk for mortality and morbidity like impaired neurodevelopmental outcomes such as cerebral palsy, mental retardation as well as more behavioural aberrations than full term-born children [16]. Hence, it is of vital importance to evade the abnormally late preterm birth to decrease both instantaneous neonatal and even the complications at advanced stage of development. This demands reliable steady treatment of prevailing and distinct risk factors. As newly reported, kidney allograft recipients have a 15-fold increased risk of preterm births and even a 7-fold higher risk for small-for-gestation births as related to the overall general population [2].

During the period of pregnancy, foetuses of such patients are exposed to immunosuppressive agents which can lead to affecting organogenesis and foetal antenatal and postnatal growth. The current evidence and recommendations are for non-usage of mycophenolate mofetil and rapamycin for 8 weeks before pregnancy because they are related to increased structural anomalies [17]. There is an extended list of immunosuppressive drugs but the drugs which are most usually used during pregnancy are steroids, tacrolimus, azathioprine and cyclosporine. Tacrolimus and cyclosporine are included in FDA category C, while steroids are included in FDA category B and azathioprine in FDA category D [17]. Short-acting glucocorticoids like prednisolone are favoured in kidney transplant patients. The use of prednisolone in pregnancy is related to higher chances for PROM and can also increase hypertension. There are cases reported of cleft palate and also cases of mental retardation have been reported associated with the use of steroids [17, 18]. Severe maternal infection can happen with augmented doses of prednisone (more than 25 mg/day). Azathioprine also has a risk of congenital anomalies and malformations that series from 5 to 11 %; but such malformations do not have any typical pattern. Azathioprine can lead to low-birth-weight babies, preterm deliveries, hyperbilirubinemia and respiratory distress syndrome. Azathioprine has been also linked with dose-related myelosuppression in the foetus.

On another pointer, the use of cyclosporine and tacrolimus during pregnancy is linked with low birth weights and increased occurrence of maternal diabetes, hypertension and kidney graft dysfunction. Cyclosporine also surges the production of thromboxane and endothelin, which are related to the pathogenesis of preeclampsia. Because of these reasons, a dose of cyclosporine must be limited to 2–4 mg/kg per day [19].

Practical recommendations for clinicians. Based on the results and implications of your study, consider providing the following recommendations:

Preconception counselling. Encourage a stable period post-transplantation before conception, ideally more than 2 years, to ensure graft stability. Optimize pre-pregnancy renal function, with serum creatinine levels below 1.5 mg/dL.

Monitoring during pregnancy. Close monitoring of renal function, blood pressure, and signs of preeclampsia during prenatal visits. Regular ultrasounds to assess foetal growth and identify complications like intrauterine growth restriction.

Medication management. Avoid teratogenic immunosuppressants like mycophenolate mofetil during pregnancy; consider safer alternatives. Monitor drug levels closely to balance graft protection with maternal and foetal safety.

Delivery planning. Plan for delivery in a tertiary care centre equipped to handle high-risk pregnancies, including NICU facilities for preterm or low-birth-weight neonates.

Postpartum follow-up. Monitor maternal renal function and graft health postpartum. Evaluate neonatal health, particularly renal function and growth parameters, during follow-up visits.

Strength of the study. This study proves to be one of its kind which is the largest series of such cases observed to date in India. All the cases were observed and managed by experienced gynaecologists and nephrologists. So, the chances of technical failure were less. All the readings were taken by a single observer to minimize interobserver's bias.

Limitations of the study. It was not a randomized controlled trial, but a retrospective observational study. So, the chances of bias can be higher. It was an observational study and there was no control group in our study. Blinding was not done so a chance of observer bias was there.

Implication of the study. This study shows that pregnancy in post-renal transplant patients is considered a high-risk pregnancy. This study proves that post-renal transplant pregnancy is possible and has good outcomes if the proper time of conceiving and modification is done according to graft functioning. From this study, one can understand the important parameters of pregnancy post-renal transplant time of commencement of immunosuppression therapy and effective patient management. One can also appreciate the critical steps in maintaining the pregnancy, and various predictors of complications in the same through this study.

Conclusions

Pregnancy in kidney transplanted patients is a high-risk pregnancy, but pregnancy does not appear to affect graft function through certain conditions. The volume of females undergoing renal transplants is swelling with time and also with longevity of life. Appropriate counselling concerning the optimal time to conceive and the effect of pregnancy on the kidney is very significant and should be modified according to graft functioning. Transplant-pregnancy interval and pre-pregnancy serum creatinine are significant factors in foreseeing pregnancy consequences. Such patients fall in a high-risk group but can have good pregnancy outcomes with regular antenatal and postnatal follow-up.

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Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

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Вагітність після трансплантації нирки: вплив на здоров'я матері та плода

Резюме. Актуальність. Вагітність у реципієнток трансплантованої нирки є високоризиковою через імуносупресію, наявні супутні захворювання і проблеми з функцією трансплантата. Оптимальні результати для матері й плода залежать від мультидисциплінарного підходу та сприятливих вихідних умов. **Мета:** визначити ідеальні умови вагітності в реципієнток трансплантованої нирки, оцінити вплив вагітності на здоров'я матері й функцію трансплантата. **Матеріали та методи.** Це було ретроспективне обсерваційне дослідження, проведене у відділенні акушерства та гінекології Інституту захворювань нирок та науково-дослідного центру (Ахмедабад, Індія) з 2014 року до листопада 2020 року. Проаналізовано 27 вагітностей у реципієнток трансплантованої нирки. Під час вагітності та після неї оцінювали нефрологічні параметри в матері, акушерські ускладнення й функцію трансплантата. Основні результати включали час між трансплантацією нирки та зачаттям, частоту народження живих дітей, ниркову функцію в матері та здоров'я новонародженого. Дані зібрані з клінічних записів і проаналізовані ретроспективно. **Результати.** Первинними кінцевими точками були інтервал між трансплантацією нирки та зачаттям, частота народження живих дітей і функція нирок матері до та після вагітності. Середній вік пацієнток на момент трансплантації становив 28,70 ± 3,82 року, середній вік на момент зачаття — 31,07 ± 2,57 року. Середній час між трансплантацією і зачаттям дорівнював 47 місяцям. Середній рівень креатиніну сироватки становив 1,13 ± 0,39 мг/дл під час зачаття й 1,09 ± 0,45 мг/дл після пологів. Шістнадцять вагітностей (59 %) завершилися народженням живих дітей. Поширеними ускладненнями були прееклампсія (6 випадків, 22,22 %), передчасні пологи (16 випадків, 59 %) та низька вага при народженні (9 випадків, 33,33 %). Кесарів розтин виконано 14 жінкам (52 %). **Висновки.** Вагітність у реципієнток трансплантованої нирки можлива при ретельному моніторингу і не має значного впливу на функцію трансплантата при дотриманні оптимальних умов. Результати залежать від адекватної функції нирок до вагітності, стабільної імуносупресивної терапії та мультидисциплінарного підходу.

Ключові слова: вагітність після трансплантації нирки; вагітність високого ризику