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Three successful pregnancies after kidney transplantation with long-term graft survival: case report

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Abstract

Pregnancies after kidney transplantation are considered high risk. Preconceive care is crucial for favorable mother-fetal outcome but also for good renal graft function.

Herein, we report a case of kidney transplant recipient secondary to lupus nephritis with three consecutive successful pregnancies and excellent graft function after 16 post-transplant years. Preconception care included two protocolar biopsies performed prior to immunosuppressive treatment modifications. No signs of rejections were found in either biopsy, no additional treatment was necessary, and the patient was safely converted from mycophenolate mofetil to azathioprine. First pregnancy was naturally conceived, its course was uncomplicated and a healthy female newborn was delivered via vaginal birth. Within one year after delivery the patient presented proteinuria, borderline changes were found in the biopsy of allograft and were treated with immunosuppression augmentation and ACEI. At 7th post implantation year, after surveillance biopsy showing no signs of rejection and appropriate pharmacotherapy adjustments, second pregnancy occurred from in vitro fertilization (IVF). It was complicated with deep vein thrombosis, intrauterine growth restriction and premature birth in 32nd week of gestation. Three months after delivery, the patient conceived spontaneously, third pregnancy course was uncomplicated. Close follow up, including protocol and indication biopsies, allowed to preserve excellent graft function in the context of multiple immunosuppressive treatment adjustments. Here we present a case where natural conception and in vitro fertilization intertwine without harming the transplanted organ.

Keywords: kidney transplant, pregnancy, biopsy

Introduction:

Pregnancies after kidney transplantation are considered high risk. Such pregnancies require planning and close monitoring by multidisciplinary team composed of obstetrician specialized in high-risk pregnancies, transplant care team and nephrologist [1,2]. Typically, preconceive care includes: optimal control of diabetes and hypertension, medication review to discontinue therapy with teratogenic effects, e.g. switching mycophenolate mofetil to azathioprine and testing for infections like CMV [1]. Maternal complications are listed as hypertension, pre-eclampsia and premature delivery; possible fetal complications as preterm birth, small for gestational age, intrauterine growth restriction [1,3].

Although successful kidney transplantation increases the chances to conceive, the rate of infertility is slightly higher than in the general population [4]. Data regarding assisted reproductive techniques (ART) in post-transplant setting is very limited, but successful outcome remains highly probable after in vitro fertilization in renal graft recipients [3,4,5,6].

Pregnancy is not associated with higher risk of rejections of the allograft in recipients with stable, good renal function in preconception period; those with elevated creatinine concentration and proteinuria have increased risk of graft dysfunction associated with pregnancy [1,2]. In women fulfilling safety criteria [2], pregnancy does threaten kidney graft and patients' survivals [7].

Recently, protocol biopsies have become a safe and effective tool to monitor transplanted kidney condition, they are conducted at predefined intervals regardless of allograft function and are used to identify and treat allograft rejection on subclinical phase [2]. Protocol biopsies also allow to detect other conditions like drug toxicity or recurrent diseases; additionally, they also provide prognostic information [2,8,9].

We report how application of safe pregnancy criteria together with surveillance and indication biopsies allowed to navigate through the threats of three high-risk pregnancies and necessary immunosuppressive treatment adjustments.

Case report:

Here we report a case of a woman with lupus nephritis and hypertension who underwent kidney transplantation at the age of 27. She tested negative for panel reactive antibodies (PRA), received the kidney from 46-year-old male donor with no HLA match and total ischemia time of 16 hours. The surgery was performed standard way. Patient received induction with Thymoglobuline (Genzyme), and the three-drug immunosuppressive therapy: steroids, cyclosporine A, and mycophenolate mofetil. Due to delayed graft function, she required two hemodialysis sessions.

During the first post-transplant year only minor complications occurred, anemia requiring temporary ESA (Erythropoiesis Stimulating Agent) application and recurrent episodes of lower urinary tract infections. The pharmacotherapy of hypertension included two medications: amlodipine and betablocker. One year after engraftment, her serum creatinine concentration was 0,9 mg/dl and no proteinuria was found.

Within second post-transplant year the patient expressed the wish to conceive, therefore she underwent preconception assessment. Serum creatine concentration was 0,9 mg/dl, ANA and antiphospholipid antibodies were negative, C3 and C4 levels were normal. The protocol biopsy before pregnancy was performed in which mild arteriosclerosis (cv1) and arteriolar hyalinosis (ah1) were present but no signs of rejection were found. After excluding rejection episode, treatment adjustment was undertaken, mycophenolate mofetil was withdrawn and azathioprine introduced, necessary adjustments in antihypertensive treatment were done.

Within six months after immunosuppressive treatment conversion, hypocomplementemia and positive ANA antibodies were observed whereas graft function remained stable. Due to those findings immunosuppression therapy was intensified (prednisone and azathioprine doses were increased). In the following months control anti-dsDNA turned out negative

Four years after transplantation the patient naturally conceived and experienced obstetric course with mild complications. High pressure was observed during second trimester, and dosage of methyl dopa was adjusted. The graft function was satisfactory- creatinine concentration was 0,7 mg/dl in first trimester and 1 mg/dl in third trimester, no proteinuria was found. The childbirth occurred via vaginal delivery at 39th week of gestation. The patient gave birth to healthy daughter with normal anthropometric parameters. After delivery immunosuppressive therapy was modified – azathioprine was changed to mycophenolate

mofetil and dosage of steroid was increased. The graft function was stable (serum creatinine 0,8 mg/dl), and the control of hypertension was good.

Four months after the pregnancy proteinuria was noticed. ANA antibodies were negative concentration of C3 and C4 normal, serum creatinine concentration 0,9mg/dl. Diagnostic biopsy was conducted, borderline changes together with moderate chronic vascular (cv2) and early chronic glomerular changes (cg1) were found. Considering biopsy outcome, persistent proteinuria, and comorbid hypertension MMF was temporarily increased to 1,5g/day, amlodipine was switched to ramipril as well as conversion from cyclosporine A to tacrolimus was undertaken. In the following months resolution of proteinuria was observed.

Two years after the first childbirth and 6 years after engraftment patient expressed a wish to conceive again and underwent subsequent preconceive assessment. In preconceive protocol biopsy there were no signs of acute rejection; mild arteriosclerosis (cv1) and arteriolar hyalinosis (ah1) were present. The graft function was excellent and immunological parameters of SLE negative. Appropriate changes in pharmacotherapy were made. After failing to conceive, infertility was diagnosed, and the patient underwent in vitro fertilization. The course of pregnancy was complicated with lower extremity deep-vein thrombosis, intrauterine growth restriction and premature birth. Serum creatine concentration increased slightly from 0,9mg/dl in the first to 1,08 mg/dl in the third trimester. At 32nd week of gestation, due to deterioration of fetal well-being and high blood pressure, cesarian section was performed, and the patient gave birth to the son with a low birth weight. During postpartum period our patient suffered from pneumonia.

Three months after the second pregnancy patient conceived spontaneously. The course of pregnancy was uneventful. Creatinine concentration during the third pregnancy was 0,8 -1 mg/dl without proteinuria. It was full-term pregnancy with favorable outcome for mother and female neonate.

In long term observation, 16 years after kidney transplantation, the patient remains generally healthy with excellent graft function of serum creatinine 0,8 mg/dl. She has well controlled hypertension treated with ramipril, metoprolol, torasemide and lercanidipine. Maintenance immunosuppressive therapy includes azathioprine, tacrolimus and steroids.

Discussion:

We present the case of three consecutive successful pregnancies after kidney transplantation with excellent long-term graft function. To monitor transplant condition before pregnancies the patient underwent two protocolar biopsies. To the best of our knowledge there are no similar reports in the literature.

Our patient received the course of thymoglobuline as a rejection prophylaxis due to no HLA match, young age at the time of transplantation, she also suffered from delayed graft function. Induction therapy is administrated at the time of kidney transplantation to minimize the risk of rejection [2]. A lymphocyte-depleting agent is recommended in individuals of high immunological risk, those with poor HLA matching, young age, old donor age, PRA or of donor specific antibodies presence, blood group incompatibility, delayed onset of graft function, cold ischemia time over 24h [2].

Protocol biopsies are conducted to detect subclinical rejection. Early treatment of rejection may prevent transplant glomerulopathy. Those biopsies are most beneficial for patients with higher risk of rejection [10]. Although there are some controversies around long-term protocol biopsies, the normal histology can indicate safety of reducing immunosuppression dosage [8]. As far as we know, there are no reports of protocolar biopsy being employed to monitor renal graft before pregnancy. In our case patient underwent protocolar biopsies twice. In both specimens mild arteriosclerosis and arteriolar hyalinosis were found, however in none of them histological sings of rejection occurred. Patient did not undergo biopsy before third pregnancy, which was unplanned as she conceived shortly after the second one. During each pregnancy the graft function was stable, there were no clinical and laboratory sings of rejections.

Four months after her first childbirth, three years after transplantation significant proteinuria od 1g/day occurred. Serum creatinine concentration was 0,9 mg/dl, ANA antibodies were negative and C3 and C4 concentrations normal. Generally, in transplant recipients with good pre-pregnancy graft function, there is no excessive risk of rejection [1,2,7]. Additionally, in our case we had to consider pregnancy-induced relapse of lupus nephritis. It was also reported that even if SLE markers: hypocomplementemia and anti-dsDNA are lacking, there is a possibility of lupus nephritis recurrence. Unjustified delay in conducting biopsy, and therefore introduction of optimal treatment, may result in chronic, irreversible lesions [11]. Our patient underwent biopsy within months after proteinuria presentation. In the specimen borderline

changes were found that were treated with mycophenolate mofetil dose increase, conversion from cyclosporine A to tacrolimus and addition of ramipril for symptomatic treatment of proteinuria. The latter vanished within four months following treatment adjustments.

Cases of successful IVF after kidney transplantation have been previously reported [3,4,5,6]. Before IVF patients must be in good health, have good graft function and well-controlled blood pressure [3]. Nevertheless, risk of maternal and fetal complications seems to be higher in pregnancies from assisted reproductive technology [3]. The most frequent complications are hypertension, preeclampsia, intrauterine growth restriction, and gestational diabetes [5]. Before her second pregnancy our patient fulfilled the criteria for safe IVF. The course of her second pregnancy was later complicated with deep vein thrombosis, intrauterine growth restriction, worsening of blood pressure control, premature birth and in the early post-partum period with pneumonia. Fortunately, after successful management of all those serious conditions, the renal graft function remained stable. Unexpectedly, three months after second childbirth, the patient conceived spontaneously. The course of third pregnancy remained uncomplicated. Spontaneous pregnancies rate among couples, who been successfully treated by IVF, is 17% [12], there are no data about natural pregnancies after IVF treatment in kidney transplant recipients. To best of our knowledge spontaneous pregnancy after secondary infertility treated with IVF in kidney recipient was never reported before.

The effect of pregnancy on transplanted kidney estimated glomerular filtration rate (eGFR) is not clear. Recently, two papers with conflicting outcomes were published. The cohort study of 197 female European transplant recipients showed that pregnancy does not influence eGFR loss and does not accelerate the post-pregnancy eGFR slope [13], whereas according to the study from the USA, pregnancy significantly affected postpartum eGFR decline [14]. More research assessing the impact of pregnancy on eGFR attrition are highly demanded.

In general, when following safety guidelines for post-transplant conception, pregnancies do not affect kidney survival [7].

The limitations of our case study should be considered:

Protocol biopsies were taken before conversion from mycophenolate mofetil to azathioprine and couple of years before conception. It provided information about a histological condition of the renal graft at immunosuppression adjustment but not during pregnancy.

In recent years it has been shown that post-transplant pregnancies may trigger *de novo* donor specific antibodies formation. Our patient's pregnancies occurred before this phenomenon was observed and thus, we could not monitor for the latter.

Conclusions:

Protocol biopsies may inform preconceive immunosuppression adjustments to lessen the risk of overlapping maneuvers on immunosuppression with preclinical phase of rejection. Effective monitoring and treatment of allograft rejection is prudent to achieve good long-term renal graft function after pregnancy. Rigorous research is needed to assess the utility of protocol biopsies in preconceive care.

Author Contributions

Conceptualization, D.P., P.R.; methodology: K.K. (Katarzyna Kosecka), A.C. and A.J.; formal analysis K.K.(Karolina Kosieradzka), A.M. and D.A.; data curation D.P., P.R. and I.Ł.; writing- original draft preparation—D.P., A.M., I.Ł., J.S.,K.K.(Karolina Kosieradzka), D.A. writing- review and editing—P.R., A.J, A.C. K.K.(Katarzyna Kosecka); supervision D.P. and P.R. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

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Informed Consent Statement

Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement

All information is publicly available and data regarding this patient can be obtained upon request from corresponding senior author.

Conflicts of Interest

The authors declare no conflict of interest.

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