Pregnancy management of women with kidney transplantation

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Abstract: Women with renal disease, besides many dysfunctions, face increasing infertility and high-risk pregnancy due to uremia and changes of the hormonal functions. After renal transplantation, sexual dysfunction improves, providing the possibility of successful pregnancy for women of childbearing age. However, kidney transplanted patients are high-risk pregnant patients with increased maternal and fetal risks, and the graft also may be compromised during pregnancy; most studies report on several successive deliveries due to multidisciplinary team management. In clinical practice, the graft is rarely affected during the period of gestation. Fetal development disorders are also rare although preterm delivery and intrauterine growth retardation are common. For now, several studies and clinical investigations proved that, under multidisciplinary control, kidney transplanted female patients are also possible to have safe pregnancy and successful delivery. There are conflicting data in the literature about the prevention of complications and the timing of pregnancy. Herein, we would like to present some experience of our centre. A total of 847 kidney transplantations have been performed between June 1993 and December 2013 with 163 childbearing aged females (18–45 years) in our center. We report on three kidney transplanted patients who have given birth to healthy newborns. In our practice, severe complications have not been observed.

Keywords: high-risk pregnancy, pregnancy management, kidney transplantation

Introduction

Female patients suffering from chronic uremia often experience infertility due to multifactorial etiology. The loss of positive feedback from estradiol results in the absence of the typical preovulatory pituitary gonadotropin lutenizing hormone (LH) surge. Besides, there is hyperprolactinaemia due to autonomous hypersecretion [1, 2]. Within 12 months after renal transplantation, sexual dysfunction improves; the patients become ovulatory and the menstruation resumes. Transplantation offers a better quality of life providing the possibility of successful pregnancy for women of childbearing age. However, kidney transplant recipients are high-risk pregnant patients with increased maternal and fetal risks, and the graft also may be compromised [3] *(Table I)*. Several clinical case reports have been published, stating that pregnancy does not seem to have adverse effects either on long-term graft or patient survival or renal function in women after renal transplantation. Fetal development disorders are also rare, though preterm delivery and intrauterine growth retardation are common [4]. Preconception counseling and timing of pregnancy are of high importance in the case of kidney transplanted patients. The data about these issues are controversial in the literature; the most often applied recommendations are summarized in *Table II*. Before conception, the level of immunosuppression should be reduced [5]. To avoid acute rejections, drug level should be monitored closely and the dosage should be modified to reach the recommended target level. Because of their teratogenic effect, mycophenolate mofetil (MMF) and sirolimus (SRL) are contraindicated; they should be withdrawn 6 weeks before planned conception. Gravid uterus may obstruct

Table I Kidney transplanted patients increased risk factors in pregnancy

Maternal complications	Fetal complications
1. Hypertension	1. Pregnancy loss (mainly I., II. trimester)
2. Preeclampsia	2. Preterm delivery
3. Allograft rejection	3. Intrauterine growth retardation (IUGR)
4. Infections	
5. Diabetes	

Table II Criteria for considering pregnancy in renal transplant recipients

1. Good general health at least 2 years after transplantation
2. Absence of other contraindications (obstetrics, etc.)
3. Stable allograft function — serum creatinine below 180 μmol/L (2 mg/dL)
4. No recent episodes of acute rejection, no evidence of ongoing rejection
5. Normal blood pressure (below 140/90 mmHg) or minimal antihypertensive regimen (one drug)
6. Absence of or minimal proteinuria (<0.5 g/day)
7. No sign of pelvicalyceal distension (abdominal ultrasound)
8. Recommended immunosuppression:
Prednisone <15 mg/day
Azathioprine <2 mg/kg/day
CsA or tacrolimus at therapeutic levels (according to blood serum level)
Close drug level monitoring
MMF and sirolimus are contraindicated because of their teratogenic effect
MMF and sirolimus should be stopped at least 6 weeks before planned conception is attempted

the graft ureter (mass effect); however, it is a rarely reported cause of allograft dysfunction in pregnancy [6]. In our center, 847 patients suffering from end stage renal disease have been transplanted till December 2013, among them 163 women of childbearing age out of 269 female patients. Three patients have decided to become pregnant until that time.

Case Report

Our first patient is a 39-year-old female renal transplant recipient with a history of end stage renal disease due to chronic glomerulonephritis and chronic pyelonephritis diagnosed in 1995. She was on hemodialysis for 3 years, and then, she had a cadaver transplant. During dialysis, she got infected with hepatitis C virus (HCV). Six years after transplantation, she delivered a normal weight healthy male newborn by Cesarean section in 2001. Preconceptionally, she was on triple therapy: cyclosporine A (CsA), methylprednisolone, and azathioprine. Six weeks before conception, azathioprine and methylprednisolone were withdrawn and the dose of CsA was reduced (150–175 mg/day). During pregnancy, the serum level of CsA was between 150 and 200 ng/mL (C0). Right after delivery, the dose of CsA was raised up to 200–225 mg/day (C0: 200–260 ng/mL), and 32 mg/day methylprednisolone was given for 3 days and then tapered to 4 mg/day. The renal function of the recipient continued to be stable after delivery. Before pregnancy, we found blood serum creatinine levels 119–125 μmol/L permanently; however, during pregnancy, a moderate elevation has been observed *(Table III)*. Despite good graft function the patient's compliance has become in-

Table III Comparison of selected nephrological parameters of our kidney transplanted patients with pregnancy

	1st Patient	2nd Patient	3rd Patient
Age at the time of pregnancy (year)	39	30	31
Serum creatinine levels 6 weeks before planned conception (μmol/L)	119–125	160–175	111–115
Serum creatinine levels during pregnancy (μmol/L)	116–140	164–174	93–110
Acute rejection observed during pregnancy	No	No	No

sufficient from 2005. By reason of that condition after several therapeutic approaches, we were forced to refer back her to the hemodialysis program in 2008. Graftectomy was performed in 2009 because of chronic allograft rejection.

Our second patient is a 30-year-old renal transplant recipient with end stage renal disease because of chronic glomerulonephritis, diagnosed as infant. She has hypertension in her history. She was not dialyzed before transplantation. She had complaints about severe left hip joint pain; the investigation performed showed avascular necrosis in the head of the femur. Core decompression was performed in 2000, and her complaints decreased permanently. Two years after surgery without any complications, she got ovulatory induction treatment, since spontaneous ovulation did not start. She had extrauterine gravidity – a possible complication of this therapy, and a laparoscopic salpingotomy was performed. Two years later, she got pregnant again and she delivered on the 28th week her premature baby per vias naturales as a result of preterm membrane rupture. The weight of the male newborn was 990 g. She was on triple therapy before the pregnancy: CsA, methylprednisolone, and MMF. Six weeks before conception, methylprednisolone and MMF were withdrawn and dose of CsA was decreased to 75–100 mg/day (C2 700–900 ng/mL). Right after delivery, CsA dosage was increased to 150–175 mg/day (C2 1100–1300 ng/mL), 32 mg/day methylprednisolone, and 500 mg/day MMF was given. There was a moderate elevation in the serum level parameters during pregnancy comparing to preconceptionally but the graft function was stable.

Our third patient is a 31-year-old female who suffered from end stage renal disease as a consequence of chronic glomerulonephritis. She was on dialysis for 1 year, when she got pregnant in 1996 and delivered a male preterm newborn by Cesarean section. Seven years later she got a kidney transplant in 2003. Two years later, she got intracranial bleeding in the thalamus. Two years later, she had transitory ischemic attack. She recovered fully. Two years later with stable graft function and good general health, she decided to become pregnant again. Medications were modified according to the international guidelines. However, she got pregnant only 2 weeks after decreasing dosage of CsA and methylprednisolone and withdrawal of MMF. Artificial abortion was offered because of the high teratogenic effect, but she refused it. Her fetus suffered missed abortion on the 6th week, and the abortion was terminated. There were no maternal complications. Then after half a year, she got pregnant. In March 2009, the patient, due to preterm membrane rupture, underwent a Cesarean section giving live birth to her 1300 g preterm male infant on the 30th week of pregnancy, with no congenital malformation. Before conception, she was on CsA 50–75 mg/day (C2 360–500 ng/mL) and methylprednisolone 4 mg/day, and MMF was withdrawn. After delivery, higher dose immunosuppression was given with CsA 50–75 mg/day (C2 500–600 ng/mL), methylprednisolone 4 mg/day, and MMF 2 × 500 mg/day. Similarly to the two other patients, we found mild elevation in the serum levels of creatinine during pregnancy.

Discussion

Renal transplantation has provided for women of childbearing age not only better quality of life but increased fertility and the possibility of successful pregnancy outcomes. However, kidney transplanted patients are high-risk pregnant patients with significant maternal, fetal, and allograft complications, due to multidisciplinary control they can give life to healthy infants [2, 3]. If the pregnancy extends beyond the first trimester, it has high probability of reaching full term [7]. One of the main maternal complication during gestation is hypertension as a result of either preexisting chronic hypertension or development of new onset hypertension during gestation [8]. Patients with well-balanced blood pressure are more likely to have succesfull delivery with healthy newborns and less likely to have maternal or fetal complications [9]. According to some major investigations, blood pressure is lowest in the first trimester during normal gestation and slowly elevates in late gestation. Similar but blunted pattern of blood pressure progression was often observed in the case of transplant recipient pregnant females [10]. Methyldopa was recommended by several studies for mild hypertension management, since it is well-tolerated and, moreover, does not alter uteroplacental or fetal hemodynamics. According to novel recomendations for urgent blood pressure control, hydralazine, labetolol, or nifedipine has been considered [11]. It is highlighted that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are absolutely contraindicated in pregnancy because of adverse fetal effects, and atenolol must be also avoided because of concerns about fetal growth found by major studies [12]. Renal transplant pregnant patients with hypertension are at increased risk for development of superimposed preeclampsia, with an incidence of 15 to 25% compared with 5% of normotensive pregnancies [13]. The incidence of acute rejection is low as found by several investigations [14]. Generally, pregnancy does not seem to have any adverse effect on the long-term graft survival of renal allografts [15]. If there is a suspicion of acute rejection based on clinical signs and symptoms, it has to be confirmed by ultrasound guided core biopsy. In the case of acute rejection, it is prudent to initial treatment with steroid. There are limited data for the use of other agents such as anti-T-lymphocyte antibodies, muromonoab-CD3, and antithymocyte globulin in the case of allograft rejection, but IVIG appears to be safe [2]. Considering

Table IV Comparison of selected obstetrical parameters of our kidney transplanted patients with pregnancy

	1st Patient	2nd Patient	3rd Patient
Way of delivery	Cesarean section	Natural	Cesarean section
Termination of delivery (week)	39	28	30
Newborn's weight (gram)	2730	990	1300
Congenital malformation	No	No	No
Previous pregnancy	No	No	1 (Missed abortion)
Gestational diabetes	No	No	No
Conception	Spontaneous	Ovulatory induction treatment	Spontaneous

the creatinine levels, we found relatively constant serum levels in the case of all our three patients.

The applied immunosuppressive drugs have many side effects, without limited information about their influence on the fetus. It is recommended to give the minimal effective dose. On the basis of some investigations, one-year-long period between renal transplantation and conception seems reasonable to stabilize renal function and reduce immunosuppressant drug doses [16]. Breast feeding is not considered to be absolutely contraindicated; however, immunosuppressants cross the placenta and appear in the breast milk to varying degrees [17]. In our clinical practice, we do not suggest breast feeding to the patients at all. Preconceptionally (at least 6 weeks before planned conception), MMF should be withdrawn or switched to azathioprine. During pregnancy, it is enough to apply decreased dose of immunosuppressants, although inadequate medication can cause acute rejection. Right after delivery, elevated immunosuppression needed and supplemented with the drugs previously interrupted. In the case of our third patient's first pregnancy after transplantation, there was not enough period of time between the modification of immunosuppression and the conception and, later, it was terminated as a missed abortion. Outcomes of unwanted pregnancies are inferior to those for planned pregnancies [18]. Congenital malformations are rare although preterm delivery and intrauterine growth retardation are common. Fetal and maternal complications *(Table I)* even can lead to more serious complications [19, 20]. Pregnancy does not appear to have adverse effects on long-term graft or patient survival or kidney function in women after renal transplantation [4]. The fact that transplantation alone does not have any effect on the way of delivery, cesarean section is not obligatory (*Tables III* and *IV*).

Considering the international guidelines and recommendations, tailored therapy should be applied to every kidney transplanted patient. Adequate preconceptional counseling and right timing of conception can give a real opportunity for kidney transplanted patients to give birth to healthy children. In Hungary, until October 2011, 3.9% of renal and 14.3% of liver transplanted fertile women gave birth to children; however, there was no pregnancy among heart, lung, and pancreas recipients. All of the newborns were healthy, and there was no acute rejection episode or graft loss due to pregnancy [21]. Although, in our center, numerous kidney transplantations were performed with low number of delivery, it seems safe to manage pregnancy under multidisciplinary medical control.

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