CASE REPORTS

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The outcome of pregnancy in a kidney transplant patient: a case report and review of the literature

Ishod trudnoće kod bolesnice sa transplantiranim bubregom: prikaz slučaja i pregled literature

Andreja Glišić*, Nevena Divac†, Miroslava Gojnić Dugalić*, Biljana Kastratović Kotlica*, Neven Vavić‡, Nataša Cerovac§, Milica Prostran†

University of Belgrade, Faculty of Medicine, Clinical Center of Serbia, *Clinic for Gynecology and Obstetrics, †Institute of Pharmacology, Clinical Pharmacology and Toxicology, Belgrade, Serbia; Military Medical Academy, ‡Center for Transplantation of Solid Organs, Belgrade, Serbia; §Clinic for Neurology and Psychiatry for Children and Youth, Belgrade, Serbia

Abstract

Introduction. The possibility of a term pregnancy with favorable maternal and neonatal outcome is one of the greatest advances in kidney transplantation, though concerns still exist regarding the safety of the mother, fetus, and graft. The use of immunosuppressive medications during pregnancy is related to possible fetal adverse effects. **Case report.** We report a course of a pregnancy in a patient with a kidney transplant. The patient was treated with immunosuppressive therapy (tacrolimus, azathioprine, and prednisolone) during the pregnancy. The outcome of the pregnancy was without maternal and neonatal complications. Serum creatinine levels were stable and no acute organ rejection occurred during pregnancy. Significant elevation of the D-dimer and coagulant factors II, VII, IX and X were noticed during the third trimester. This could be partially attributed to azathioprine, which was a part of the immunosuppressive regimen. On the other hand, there were no radiological or clinical signs of thromboembolism, but low-molecular-weight heparin prophylaxis was immediately initiated. Cesarean section was performed at the 39th gestational week and a healthy female infant was delivered with a birth weight of 3,150 g and Apgar score 9. **Conclusion.** Pregnancies of kidney transplant recipients are high-risk and require a multidisciplinary approach. Careful clinical follow-up is a prerequisite for favorable outcome.

Key words:
kidney transplantation; pregnancy; fetal development; tacrolimus; azathioprine; prednisolone.

Apstrakt

Uvod. Mogućnost uspešne trudnoće kod žena sa presađenim bubregom smatra se jednim od najvećih uspeha ove vrste lečenja, ali nosi sa sobom i određene probleme u vezi sa bezbednošću majke, fetusa i presađenog organa. Upotreba imunosupresivne terapije tokom trudnoće povezana je sa mnogim neželjenim efektima. **Prikaz slučaja.** Prikazali smo bolesnicu sa presađenim bubregom koja je tokom trudnoće primala imunosupresivnu terapiju (takrolimus, azatioprin i prednizolon). Ishod trudnoće je bio uspešan i po majku i po novorođenče. Nivo serumskog kreatinina majke bio je stabilan sve vreme trudnoće i nije doslo do akutnog odbacivanja presađenog organa. Tokom trećeg trimestra došlo je do neuobičajenog porasta D-dimera i faktora koagulacije II, VII, IX i X, što je retka, ali moguća komplikacija primene azatioprina. Nije bilo kliničkih niti radioloških znakova tromboembolizma, ali je niskomolekularni heparin uveden profilaktički. Trudnoća je završena u 39-oj nedelji gestacije planiranim carskim rezom i rođeno je zdravo žensko dete porođajne težine 3 150 g, ocenjeno Apgar skorom 9. **Zaključak.** Trudnoća kod bolesnice sa presađenim bubregom smatra se visoko rizičnom i zahteva pažljivo planiranje i praćenje.

Ključne reči:
transplantacija bubrega; trudnoća; trudnoća, razvoj fetusa; takrolimus; azatioprin; prednizolon.

Correspondence to: Nevena Divac, University of Belgrade, Faculty of Medicine, Institute of Pharmacology, Clinical Pharmacology and Toxicology, Dr Subotića 1, 11 000 Belgrade, Serbia. Phone: +381 11 616 1746. E-mail: ndivac@med.bg.ac.rs

Introduction

The impaired reproductive function is one of the detrimental consequences of end-stage renal disease (ESRD). The restoration of pituitary-ovarian function and fertility in female kidney transplant recipients is one of the greatest achievements of modern transplantation. The first report of a pregnancy in a kidney transplant recipient was published in 1958. After that, due to the improvement of immunosuppressive therapy and modern perinatal care, series of pregnancies with favorable outcomes have been reported worldwide [1–3]. The pregnancy in a kidney transplant patient is complicated due to previous major abdominal surgery, pre-existing comorbidities such as diabetes, hypertension etc, and the adverse effects of immunosuppressive treatment [3]. Pregnancy complications associated with chronic renal failure, such as hypertension, proteinuria, preeclampsia and preterm delivery, are still possible in kidney transplant recipients. These pregnancies are always considered as high-risk and deserve careful planning and clinical follow-up from the very beginning.

Immunosuppressive medications prevent kidney rejection but also carry significant risks. During pregnancy, these medications are related to many serious fetal adverse effects. Therefore, it is important to carefully evaluate the safety and efficacy of immunosuppressive medication during pregnancy and to provide adequate clinical prenatal care in order to reduce the risk of graft rejection on one side, and unwanted effects on fetal development on the other side.

The present study is a review of a new case of a pregnancy in a kidney transplant recipient treated with tacrolimus, azathioprine, and prednisolone, with successful maternal and fetal outcome. There have been very few reports of such pregnancies in Serbia.

Case report

The patient was a 26 year old pregnant woman with the history of kidney disease. She was diagnosed with ESRD eight years ago. Hemodialysis was initiated three years later. After eight months of dialysis, she was transplanted a living related donor kidney at the Military Medical Academy in Belgrade. The procedure was performed successfully and the patient was discharged on the 23rd post-transplantation day with serum creatinine level of 161 μmol/L. The clinical protocol included immunosuppressive treatment comprising tacrolimus, prednisolone and mycophenolate mofetil. Antihypertensive therapy was prescribed (metoprolol and nifedipine) and on discharge, her blood pressure was within recommended values for kidney transplant patients [4]. The patient was followed-up at regular intervals and the doses of immunosuppressive drugs were gradually tapered to maintenance doses.

Three years later, the patients spontaneously conceived. She was referred to the Clinic of Gynaecology and Obstetrics, Clinical Center of Serbia at 5 weeks gestation. Since pregnancies in transplant patients require a multidisciplinary approach, a close cooperation with nephrologists from the Military Medical Academy was established. Her immunosuppressive regimen was changed to tacrolimus 3.5 mg in the morning and 3.5 mg in the evening, prednisolone 7.5 mg/day and azathioprine 50 mg/day. Mycophenolate mofetil was stopped. Beta blocker was also withdrawn, verapamil was introduced and methyldopa continued. The patient was followed on monthly basis throughout the entire pregnancy. Ultrasonographic examinations showed normal fetal growth and amniotic fluid volume was in the normal range. The laboratory values of serum glucose, electrolytes, serum urea and creatinine, proteins in 24-hour urine collection and protein to creatinine ratio were regularly controlled. The serum creatinine levels throughout the course of pregnancy were stable between 79–110 μmol/L and the day before the cesarean section it was 116 μmol/L. The urine protein to creatinine ratio was stable in range 0.38–0.41. Blood pressure was well controlled with methyldopa and verapamil.

The patient's coagulation status was also closely monitored. During her third trimester, D-dimer and coagulation factors (II, VII, VIII, IX and X) were elevated. D-dimer levels were between 3.13 to 4.38 mg/L. The left-sided leg edema also developed. The lower-extremity venous duplex ultrasound was performed, and she was found to have no signs of deep venous thrombosis (DVT) or superficial thrombophlebitis. However, it was decided that anticoagulant prophylaxis should be started and low molecular weight heparin (fraxiparine) was initiated. Asymptomatic bacteriuria was treated by ceftriaxone 2g /daily i.m. during ten days.

We performed planned caesarean delivery because the transplant kidney was located very low in the pelvis and probably could obstruct the labor.

A healthy female child was born at term by caesarean section. Birth weight was 3,150 g, Apgar score 9 at first minute of life and no congenital malformations were identified. Neurological and clinical status of the baby at birth was normal. During first months of life, the baby achieved age-appropriate developmental milestones. During the early postoperative period, the patient's serum creatinine level showed transient elevation up to 218 μmol/L but reverted to baseline values. We performed intravenous hydration (3,000 mL of fluid *per* a day) during 7 days. There were no signs of acute kidney rejection. The patient was advised against breastfeeding and bromocriptine was administered to terminate lactation.

Discussion

Pregnancy in kidney transplant recipients is burdened with risks and requires careful follow-up. These risks include impaired renal function, graft rejection, spontaneous abortion, preterm delivery, low birth weight and fetal growth retardation [5]. Great concern in such pregnancy is the potential adverse effect of immunosuppressant drugs to the fetus.

The recommended immunosuppressive regimen in pregnant kidney transplant recipients usually comprises a calcineurin inhibitor, corticosteroid and azathioprine [6]. Mycophenolate mofetil and mammalian target of rapamycin inhibitors (mTOR) are associated with increased incidence of spontaneous abortions and congenital malformations in fetuses [7, 8].

Therefore, these two drugs are not recommended during pregnancy and should be discontinued before conception, or, if the pregnancy was not planned, immediately after [7, 9].

Tacrolimus belongs to a class of calcineurin inhibitors, together with cyclosporine. It falls into pregnancy category C by the U.S. Food and Drug Administration (FDA). Tacrolimus is preferred over cyclosporine due to better efficacy regarding graft function and graft survival [10]. Additionally, compared to tacrolimus, cyclosporine in pregnant women is associated with higher incidence of hypertension [11]. Fetal levels of cyclosporine are similar to maternal levels, whereas the umbilical cord concentration of tacrolimus is 19% of maternal unbound plasma concentration. The lower fetal concentration of tacrolimus is attributed to the active efflux of tacrolimus from the fetus toward the mother by placental P-glycoprotein activity [12, 13]. Tacrolimus has been reported to cause hyperkalemia and kidney impairment in neonates, as well as premature delivery and preeclampsia [13, 14]. Teratogenicity in children whose mothers were treated with tacrolimus during pregnancy is not significantly increased compared to general population [15, 16].

Prednisone has been widely used in pregnancy for indications other than solid organ transplantations. It is listed as pregnancy category C by the FDA [17]. Fully developed placenta partially protects the fetus from prednisone exposure by its metabolic activity (enzyme 11-beta-hydroxylase) [18]. The maternal to cord blood ratio of prednisone is 8 : 1 to 10 : 1 [19]. However, the risk of neonatal adrenal insufficiency cannot be ruled out even with low doses of prednisone and careful post-natal monitoring is required.

Azathioprine and its active metabolite, 6-mercaptopurine, are purine analogues which interfere with the synthesis of adenine and guanine ribonucleosides [20]. Azathioprine has been labeled as pregnancy category D by FDA [21]. It crosses the placenta. However, the fetus cannot metabolize it to its active metabolite 6-mercaptopurine due to lack of liver enzymes [22]. Azathioprine can cause hematological disturbances and immunodeficiency in the fetus [11, 23]. The frequency of congenital abnormalities in infants of kidney transplant recipient mothers was between 0.0–11.8% in different case-series studies [20]. The prospective, controlled cohort study by Goldstein et al. [24] which compared pregnancy outcome in women exposed to azathioprine (n = 189) to non-exposed controls (n = 230) showed no difference in terms of teratogenicity. However, the azathioprine exposed group had a higher incidence of low birth weight and prematurity.

Additionally, increased thrombotic complications in kidney transplant recipients have been associated with the use of azathioprine [25]. One of the postulated mechanisms for this is the stimulation the synthesis of coagulation factors induced by azathioprine, especially factors II and X [26]. It could partially explain the elevation of coagulation factors in our patient.

In women with a renal transplant, the cesarean delivery rate approaches 50% [27]. We performed planned caesarean delivery. Transplant kidney was located very low in pelvis near to bladder and a low segment of uterus. We made a medial abdominal incision and medial uterine incision to protect the transplanted kidney. Probably, the transplanted kidney could obstruct the labor.

Our case emphasizes the significance of a multidisciplinary approach to a pregnancy in a kidney transplant recipient. Due to excellent coordination between gynecologists, nephrologists, pediatricians and clinical pharmacologists, our patient had a successful pregnancy with favorable maternal, fetal and graft outcome. The graft function remained stable as well as blood pressure and other clinically significant parameters in the mother. The pregnancy was a full-term without postpartum complications. The baby was born without congenital malformations and with normal neurological status. Undoubtedly, the use of immunosuppressants in pregnancy requires careful planning and monitoring in order to minimize risks and enable favorable outcome.

Conclusion

Pregnancies of kidney transplant recipients are high-risk and require a multidisciplinary approach. Careful clinical follow-up is a prerequisite for a favorable outcome.

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