Annals of Gynecology and Obstetrics Research

Case Report
Published: 22 May, 2018

Pregnancy Following Kidney Transplant: Case Report and Literature Review

Tibeică Alexandra-Maria[2], Ursache Alexandra[2], Tănase Adina-Elena[2], Berescu Anca[2], Petică Mirabela[2] and Onofriescu Mircea[1,2]*

[1]Department of Obstetrics and Gynecology, Grigore T. Popa University of Medicine and Pharmacy, Romania

[2]Department of Obstetrics and Gynecology, Obstetrics and Gynecology Hospital Cuza Voda, România

Abstract

Pregnancies in women with chronic kidney failure are considered as high-risk pregnancies because there are some possible complications that may occur during pregnancy and may affect the mother, the foetus, or both of them. We present the result of a successful case both for the mother and for the baby, as well as the effects of pregnancy on the function of the transplanted kidney and hemodynamics. We describe the effects of pregnancy on renal function and the effects of renal disease on the foetus. The 36-year-old patient, with a background of recurrent urinary infections and hypertension, was initially introduced to the nephrology department for investigating bilateral renal dysplasia for which peritoneal dialysis was initiated. The patient underwent dialysis for 4 years and then received renal transplantation from a donor. Prior to transplantation, she received antihypertensive treatment for 5 years and eventually developed end-stage renal disease. After the transplantation, the renal functional tests were normal and the patient did not experience any hypertension. The patient was registered at 12 weeks with amenorrhea, with BP (blood pressure) within normal range, normal kidney function, absence of proteinuria. Throughout the pregnancy, the patient consistently received immunotherapy with cyclosporine 75 mg x^2/day, and the serum concentration of cyclosporine was periodically monitored to track the need for dose adjustment, with a level of A_C2 = 302.7ng/ml at 15 weeks and 286ng/ml at 35 weeks, Imuran 50mg x^2/day, Prednisone 5mg/day, Mecopar 2 caps/day, Silymarin 3 caps/day, vit. D3 1 cap/day, Elevit 1 cap x^2/ day, Folic Acid 5mg x^2/day. At 32 weeks, it was initiated a treatment for foetal lung maturity with Dexamethasone ¾ ampoule every 12 hours, for 48 hours. At 35 weeks, there was evidence of chronic immunosuppression, mixed dyslipidaemia, asymptomatic hyperuricemia, normocytic normochromic anaemia. TOTHEMA 1cap x^2/day is added to the daily treatment. The CTG exam reveals an average heart rate of 140 BPM with good variability, the presence of accelerations and the absence of significant decelerations. At 37 weeks, due to the increase in BP values - despite the treatment with Nifedipine - and the increase of proteinuria and uric acid, C section was performed, resulting in a single living newborn male, W = 2900g, APGAR = 9. Bilateral tubal ligation was performed at the request of the patient. Post-procedure treatment was given, Dostinex 1/2 cap every 12 hours for ablactating, Dopegyt 1cap/6h for BP control, Innohep 1 ampoule /day for anticoagulation, Cefotax 2gx 12 hours. The patient is discharged in good general health state, afebrile, physiologically underdeveloped uterus, lochia in normal quantity and appearance, BP and P within normal physiological parameters.

Keywords: renal transplant; arterial hypertension; infertility

OPEN ACCESS

Correspondence:
Tibeică Alexandra-Maria, Department of Obstetrics and Gynecology, Obstetrics and Gynecology Hospital Cuza Voda, România,
E-mail: alexandra.tibeica@yahoo.ro

Received Date: *26 Mar 2018*
Accepted Date: *15 May 2018*
Published Date: *22 May 2018*

Citation:
Alexandra-Maria T, Alexandra U, Adina-Elena T, Anca B, Mirabela P, Mircea O. Pregnancy Following Kidney Transplant: Case Report and Literature Review. Ann Gynecol Obstetr Res. 2018; 1(1): 1003.

Introduction

Patients with end-stage renal disease present sexual dysfunction and infertility as a result of endocrine and vasomotor dysfunctions, use of medications, and psychological factors. Female infertility results from a change in the hypothalamic function and it is associated with increased FSH, LH, Prolactin. Hormonal changes have been corrected after kidney transplantation and will result in normal ovulation and regular menstrual cycles. Pregnancy is less common patients with renal transplant. Pregnant women with chronic kidney failure are considered as high-risk pregnancies due to some complications that may occur during pregnancy and that can affect the mother, the foetus, or both of them. We present a case of a successfully completed pregnancy for both the mother and her baby. We describe the effects of pregnancy on renal function and the effects of kidney disease on the foetus.

Case Presentation

A 36-year-old patient, with a background of a low segment transverse cesarean section performed in 2008, of recurrent urinary infections and hypertension, presented herself initially to the nephrology department for the investigation of bilateral renal dysplasia for which peritoneal dialysis has been initiated. The patient underwent dialysis between 2008 and 2011 and received a kidney transplant from a donor in 2011. Prior to transplantation, she received antihypertensive treatment for 5 years and eventually developed end-stage kidney disease. After kidney transplantation, renal functional tests were normal, and the patient did not longer present hypertension. In April 2016, the patient came to the clinic for gynecological assessment, complaining of a 12-week long amenorrhea and complicated urinary tract infection. The pregnancy test performed on that day was positive, BP was within normal range, kidney function was normal, proteinuria absent, and urinalysis results were abnormal. Treatment was initiated, consisting of antibiotic therapy with Cefuroxime, immunotherapy with Cyclosporine 75mg x^2/day, Imuran 50mg x^2/day, Prednisone 5mg, Mecorar 2 caps/day, Silymarin 3 caps /day, vitamin D3, Zinnat 250mg x^2/day for 14 days, Uractiv Mami 1cap x^2/day for 14 day. In May, 2016, a normocytic normochromic anemia was detected, the patient presenting HGB = 10.9g/dL, PLT = 227 * 000/microL and ESR = 80 mm/h. The immunological tests revealed cyclosporine A_C2 = 302.7 ng/ml. The double test revealed low biochemical risk and age-related risk for Down, Edward, and Patau Syndromes, and BP within normal range. In June, 2016, it was noticed that erythrocyte parameters and PLT count returned to normal, but were lower compared to the previous examination, decreased lymphocyte counts (14.4%), urine culture> 100 000 CFU/ml mixed contamination flora. In August, 2016, anemia was detected with HGB = 10.5g/dL, HCT = 32.8%, normal PLT count, but lower compared to the previous examination (193 * 1000/microL), ESR = 70mm/h, blood biochemistry, urinalysis, and BP of normal values. In September, 2016, at 23 weeks pregnant, the patient was admitted to the nephrology clinic and the performed tests revealed: HGB = 9.8mg/dL, HCT = 31%, PLT = 112 * 1000/microL (pathological level), ESR = 94mm/h, normal urinalysis, without proteinuria, no hyperhydration phenomena, and dyslipidemia, urea, creatinine, blood glucose, uric acid, TGO, TGP and TA within normal ranges. The recommended treatment was: Cyclosporine75mgx^2/day, Imuran 50mgx2/day, Prednisone 5mg/day, Mecopar 2caps/day, Silymarin 1capx^3/day, Vitamine D3 1cap/day, Elevit 1capx^2/day, Folic Acid 5mgx^2/day. In October, 2016, the ultrasound exam showed: anterior placenta 2^{nd}-3^{rd} degree maturation, cervical length 38 mm, Doppler: MCA (middle cerebral arterial Doppler) : RI (resistive index) = 1.85, PI (pulsative index) = 1.35; AO (aorta) = 0.75, AFI (amniotic fluid index) = 13, DBP = 83mm-33s+5z; CC = 277mm-30s + 3z, CA = 289mm-33s, average W = 2144g, GA (gestational age) = 32w + 6d. Pathological laboratory findings: high uric acid level = 6.27, APTT = 24, ESR = 60mm/h. During admission, treatment was established for foetal lung maturation with Dexamethasone ¾ ampoule every 12 hours for 48 hours. The patient was discharged in good general state, normal uterine tone. Since pregnancy 35 weeks the patient was monitored weekly until delivery. Chronic immunosuppressions, mixed dyslipidemia, asymptomatic hyperuricemia, normocytic normochromic anemia were found. The immunological tests at 35 weeks gestation revealed Cyclosporine A_C2 = 286ng/mL. Urinalysis was normal, proteinuria absent and pulmonary stethacoustic parameters were normal. On November 16, 2016, at 37 weeks gestation, with the diagnosis of IIG IIP 37 Weeks, Head Presentation, Intact Membranes, Maternal Kidney Transplant, Uterine Scar After Previous C-Section. The patient gave birth via C-section to a living baby boy, W = 2900g, APGAR = 9, nuchal cord. Bilateral tubal ligation was performed at patient's request. Ablation was initiated with Dostinex 1/2cap at 12 hours, blood pressure control with Dopegyt 1cap/6hs, anticoagulation treatment with Innohep 1 ampoule/day, and antibiotic treatment with Cefotax2g/12 hours. The patient was discharged in good general health state, afebrile, with physiologically underdeveloped uterus.

Discussions

There are 2 questions to ask when a kidney transplant woman becomes pregnant:

- What is the effect of pregnancy on kidney disease?

- What is the effect of kidney disease on pregnancy?

Effects of Pregnancy on Kidney Graft Function

The long-term effect of pregnancy on kidney graft function is a main concern. Several studies have determined serum creatinine levels before and after pregnancy. Pregnant women with mild Chronic Kidney Disease (CKD) (creatinine <1.3 mg/dL) did not experience worsening of renal function. Patients with moderate CKD (serum creatinine 1.3-1.9mg/dL) experienced worsening of renal function, some developing advanced kidney disease.

Davidson et al. have demonstrated that serum creatinine> 1.5mg/dL and proteinuria> 500mg/24h significantly increase the risk of a decline in kidney graft function as a result of the effect of pregnancy on renal function [1-16]. As a result of changes in blood volume, maintenance of immunosuppressive medication dosing can be difficult, and vigilance of serum immunosuppressive levels is recommended. Data from the National Transplantation Registry (NTPR) suggest that higher doses of immunosuppressive drugs are needed to maintain kidney graft function. The recommendation of the American Society of Transplantation is that in order to avoid graft rejection, immunosuppressive drug dosing should be watched closely and frequent monitoring of serum drug levels is compulsory. Pregnancy induces hyper filtration in the transplanted kidneys, as it happens in normal kidneys during pregnancy. Therefore, detection of organ rejection can be very difficult by monitoring changes in serum creatinine levels. If organ rejection is suspected, the kidney can be safely biopsied under ultrasound guidance. If organ rejection is confirmed, it can be treated with corticosteroids. There are few data on the treatment of organ rejection with other drugs such as OKT3 oranti-thymocyteglobulin [1]. Another concern is Hypertension (HT) during pregnancy as a result of pre-existing chronic HT or HT developed during gestation [10]. In normal pregnancies, BP is the lowest in the first trimester but returns to prepregnancy levels in late pregnancy. Women with kidney transplantation experience a similar pattern. Therapeutic targets in women with mild to moderate CKD have not been established, but recommendations have been made for treatment at BP levels > 150/90mmHg. Optimal choice of antihypertensive therapy depends on the severity of hypertension. For mild HTA, methyldopa has been proposed because it is well tolerated and does not affect the uteroplacental or foetal hemodynamics. Other antihypertensive drugs that are considered acceptable include labetalol, nifedipine, and thiazide diuretics. For urgent BP control, Hidralazine, Labetalalol and Nifedipine have been used as drugs

of choice. ACE inhibitors and angiotensin receptor blockers are contraindicated during pregnancy because of their adverse foetal effects, and atenolol should be avoided as it affects foetal growth [2]. Women with CKD are at higher risk of developing preeclampsia, with an incidence of 15-25% compared with 5% in normotensive pregnancies. Preeclampsia causes severe maternal and foetal complications, such as renal failure, HELLP syndrome (haemolysis, elevated liver enzymes, and thrombocytopenia), seizures, liver failure, stroke, maternal death. For the foetus, the effects of preeclampsia are Small for Gestational Age (SGA), preterm delivery, hypoxic neurologic injury, death. The diagnosis of preeclampsia is difficult in pregnant kidney transplant recipients because BP increases late during pregnancy and many patients have pre-existing proteinuria [16]. Moreover, hyperuricemia and oedema are often coexistent in kidney transplant recipients [8]. Interestingly the histological examination and molecular information show that preeclampsia is a disorder of placental hypoxia and endothelial dysfunction, although many mechanisms are still unknown. Other comorbidities to be considered in gravid kidney transplant recipients include: gestational diabetes mellitus, anaemia, infections. As allograft recipients are at increased risk of gestational diabetes mellitus, they should be screened every trimester with a 50-g oral glucose load [15,16]. Pregnant kidney transplant recipients are at increased risk for infections due to the use of immunosuppressive drugs. Maternal-foetal transmission of infectious agents should be considered both in the mother and in the foetus. Cytomegalovirus (CMV) infection is particularly severe because it is associated with hearing and vision loss, and mental retardation and can be transmitted from mother to foetus through a transplacental route, as well as during delivery and breastfeeding. Unfortunately, the presence of maternal immunity does not absolutely protect the foetus, but reduces the risk of transmission. Antiviral medication has not been recommended during pregnancy. Other infections include: toxoplasmosis, primary herpes simplex infection, primary varicella infection, HIV infection, hepatitis B and hepatitis C virus infection. Prenatal screening can detect each of these infections, but in most cases the mother presents before prenatal screening when maternal prophylaxis is no longer possible [5].

Effects of Renal Function on the Foetus

Determining the pregnancy risks from the foetus perspective requires taking into account the length of gestation, maternal health, transmission of infections, and the effects of immunosuppressive medication on organogenesis and foetal maturation. It was found that there is an increased risk of premature birth (<37wk) and low birth weight (<2500g). Most deliveries occur because of maternal or foetal compromise, rather than spontaneous preterm labour. Kidney transplant patients are at increased risk of premature rupture of the membranes, which also contributes to increased risk of preterm birth as pyelonephritis or acute allograft rejection do [1]. The mean gestational age at delivery in renal transplant patients is 34 weeks [3]; 50% of infants have low birth weight, and approximately 22% have very low birth weight (<1500g) [6]. Because of the risk of premature delivery, steroids can be administered between weeks 28-34 to promote lung maturation if there is any sign of foetal compromise. This recommendation is applicable to foetuses with intrauterine growth restriction (IUGR) because there is a high rate of associated perinatal mortality [9]. The incidence of IUGR in renal transplant patients ranges from 30 to 50% and is considered secondary to existing HT, kidney disease and to the propensity of these women to develop preeclampsia. It is therefore advisable to closely monitor foetal growth in women with kidney transplant [13]. The consequences of low and very low birth weight for the foetus are substantial and include neurological, endocrine, cardiac, renal abnormalities.

Prospective assessments of childhood developmental have been done in infants born to kidney transplant mothers. Data from the NTPR are limited but suggest that developmental delays were seen in up to 26% of children after the age of 5 years [1]. A major concern for the foetus is the potential effects of in utero exposure to medication during organogenesis and foetal development. In-utero exposure to Mycophenolate Mofetil (MMF) has been associated with severe structural malformations. Information on sirolimus is limited. It is difficult to tell which agent is responsible for congenital defects because patients often take more than one immunosuppressive agent [11]. Calcineurin Inhibitors (CNI) are involved in the development of self-reactive T cells in foetal thymus. By blocking the normal development of T cells, CNI has been shown to block the normal process by which auto reactive T-cells are eliminated during thymus development, resulting in autoimmunity in animal models. If CNI exposure increases the likelihood of autoimmunity in children of kidney transplant mothers is not known, although a case report suggested that such an association may exist [7]. All immunosuppressive drugs have been detected to varying degrees in placental or foetal circulation [6]. Exposure to immunosuppressive drugs may continue after delivery if the mother opts to breastfeed. The American Academy of Pediatrics supports breastfeeding for mothers who take prednisone and advises against it for those who are taking cyclosporine. There are no specific recommendations for those taking azathioprine or tacrolimus. Prednisone and azathioprine are detected in breast milk in small amounts, but there are no data for MMF and sicrolimus. Until studies on the pharmacokinetics and excretion of these drugs in breast milk are conducted, the consensus of experts is that breastfeeding should not be contraindicated. The impact of foetal exposure to immunosuppressive medication during the foetal development is quantified by the presence of major structural malformations at birth. Data from NTPR suggest that the incidence of major malformations is not much higher than in the general population [14].

Particularity of the Case

Patients with CKD have infertility as a result of altered hypothalamic function. Hormonal changes are corrected after transplantation, resulting in normal ovulation cycles and regular menses [12]. Pregnancy is uncommon in kidney transplant patients, and the time between transplantation and getting pregnant is also very important for having normal kidney function tests and proper dosing of immunosuppressive medication. Thus, the risks of infection, organ rejection and HT are greatly reduced. Given that the time elapsed between renal transplantation and pregnancy was> 2 years, in our patient the pregnancy lasted up to 37 weeks without complications. If the function of the transplanted kidney is good and the patient does not show signs of hypertension or diabetes mellitus, or clinical signs of organ rejection, the pregnancy is most likely to evolve without complication up to an older gestational age.

References

1. Deshpande NA, James NT, Kucirka LM, Boyarsky BJ, Garonzik-Wang JM, Montgomery RA, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. Am J Transplant. 2011;11(11):2388-404.

2. Gerlei Z, Wettstein D, Rigo´ J. Childbirth after organ transplantation in Hungary. Transplant Proc. 2011;43:1223.

3. Kociszewska-Najman B, Pietrzak B, Cyganek A, Szpotanska-Sikorska M, Schreiber-Zamora J, Jabiry-Zieniewicz Z, et al. Intrauterine hypotrophy and premature births in neonates delivered by female renal and liver transplant recipients. Transplant Proc. 2011;43(8):3048-51.

4. Wielgos M, Szpotanska-Sikorska M, Mazanowska N, Bomba-Opon D, Kociszewska-Najman B, Jabiry-Zieniewicz Z, et al. Pregnancy risk in female kidney and liver recipients: a retrospective comparative study. J Matern Fetal Neonatal Med. 2012;25(7):1090-5.

5. Dhonnchu TN, Regan C, Egan JJ. Successful pregnancy outcome in a patient following heart, lung and renal transplant. Transpl Int. 2012;25:e43.

6. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The ''great obstetrical syndromes'' are associated with disorders of deep placentation. Am J Obstet Gynecol. 2011;204(3):193.

7. Abou-Jaoude P, Dubourg L, Bessenay L. What about the renal function during childhood of children born from dialysed mothers? Nephrol Dial Transplant. 2012;27:2365.

8. Stevens DU, Al-Nasiry S, Bulten J, Spaanderman ME. Decidual vasculopathy and adverse perinatal outcome in preeclamptic pregnancy. Placenta. 2012;33(8):630-3.

9. Hladunewich M, Hercz AE, Keunen J, Chan C, Pierratos A. Pregnancy in end stage renal disease. Semin Dial. 2011;24:634-9.

10. Wang GC, Zheng JH, Xu LG, Min ZL, Zhu YH, Qi J, et al. Measurements of serum pituitary-gonadal hormones and investigation of sexual and reproductive functions in kidney transplant recipients. Int J Nephrol. 2010;2010:612126.

11. Murray JE. Edith Helm (April 29, 1935-April 4, 2011): the world's longest surviving transplant recipient. Am J Transplant. 2011;11(7):1545-6.

12. Concepcion BP, Schaefer HM. Caring for the pregnant kidney transplant recipient. Clin Transplant. 2011;25(6):821-9.

13. Kuo HT, Sampaio MS, Vincenti F, Bunnapradist S. Associations of pretransplant diabetes mellitus, new-onset diabetes after transplant, and acute rejection with transplant outcomes: an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database. Am J Kidney Dis. 2010;56(6):1127-39.

14. Lindheimer MD, Kanter D. Interpreting abnormal proteinuria in pregnancy: the need for a more pathophysiological approach. Obstet Gynecol. 2010;115(2 Pt 1):365-75.

15. Barroso F, Allard S, Kahan BC, Connolly C, Smethurst H, Choo L, et al. Prevalence of maternal anaemia and its predictors: a multi-centre study. Eur J Obstet Gynecol Reprod Biol. 2011;159(1):99-105.

16. Davison JM, Bailey DJ. Pregnancy following renal transplantation. J Obstet Gynaecol Res. 2003;29:227-233.