Pregnancy After Renal Transplantation: Report of Five Cases and Literature Review

RENAL TRANSPLANT SONRASI GEBELİK:
BEŞ OLGUNUN SUNULMASI VE LİTERATÜR DERLEMESİ

Fatih ŞENDAĞ*, Mustafa Coşan TEREK*, Gürsen GÜNDEM*

*Dept. of Obstetrics and Gynecology, Medical School of Ege University, İzmir/TURKEY

──────── **Summary** ────────

Objective: A significant portion of women at childbearing age with a functioning renal transplant becomes pregnant. Our goal was to present a case series of pregnancy after renal transplantation.

Institution: Ege University Faculty of Medicine Department of Obstetrics and Gynecology, İzmir, Turkey.

Material and Methods: We retrospectively analyzed the outcome of pregnancies in renal transplant patients in our institute from the medical records between 1998 and 2000 and reviewed the current literature.

Results: We observed hypertension in all of the five patients. Preterm premature rupture of membranes was observed in one patient with 24 weeks of pregnancy resulting in neonatal death after vaginal delivery. The same patient also experienced acute graft rejection. Intrauterine growth restriction was observed in one patient with 33 gestational weeks of pregnancy. Fetal malformations were not observed. Eighty percent (4/5) of the patients tolerated the pregnancy well without any renal graft dysfunction. Cesarean section was performed in four out of five patients because of obstetrical indications.

Conclusion: Management of pregnancies in renal transplant patients require attention to serial assessment of renal function, diagnosis and treatment of rejection, blood pressure control, early diagnosis or prevention of anemia, treatment of any infection, and meticulous assessment of fetal well-being.

Key Words: Pregnancy, Renal transplant

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──────── **Özet** ────────

Amaç: Doğum çağındaki renal transplant hastalarının önemli bir kısmı gebe kalmaktadır. Bu çalışmanın amacı renal transplant sonrası gebe kalan bir olgu serisinin sunulmasıdır.

Çalışmanın Yapıldığı Yer: Ege Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum AD, İzmir, Türkiye.

Gereç ve Yöntem: Kliniğimizde 1998 ile 2000 yılları arasında gebe olarak izlenen renal transplant hastalarının tıbbi kayıtları retrospektif olarak incelenmiş ve son literatür ile ilgili bilgiler derlenmiştir.

Bulgular: Hastaların beşinde de hipertansiyon izlenmiştir. Preterm prematür rüptür sonrası vajinal doğum yapan 24 haftalık gebede neonatal ölüm saptandı. Aynı hastada akut graft rejeksiyonu gelişti. Otuz üç haftalık diğer bir gebelikte intrauterin gelişme geriliği saptandı. Fetal malformasyon hiçbir bebekte izlenmedi. Yüzde seksen hasta (4/5) gebeliği iyi tolere etti ve renal graft disfonksiyonu gelişmedi. Beş hastanın dördünde obstetrik nedenlerle sezaryen ile doğum uygulandı.

Sonuç: Renal transplant hastalarının yönetiminde, renal fonksiyon izlenmeli, rejeksiyon gelişirse erken tanısı konup tedavi edilmeli, kan basıncı kontrolü yapılmalı, aneminin erken tanısı konup önlenmeli, enfeksiyon erken tedavi edilmeli ve fetusun intrauterin durumu çok iyi değerlendirilmelidir.

Anahtar Kelimeler: Gebelik, Renal transplant

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For many women with renal failure, achieving pregnancy is a significant problem. Infertility and/or menstrual irregularity are common in patients with chronic renal disease. The major cause of these problems is the hypogonadotrophic hypogonadism that accompanies renal failure from any cause. For this reason, pregnancy is rare in patients with chronic renal failure, and successful pregnancy is almost unheard of in dialysis-dependent patients. Renal transplantation for end-stage kidney failure has become common. The first-year survival for matched familial donor grafts is 7 to 90 percent, and ovulation promptly returns in most women. After transplantation, renal and endocrine functions return rapidly and normal sexual activity can ensue. A significant portion of women at childbearing age

Table 1. Perinatal outcome in pregnant patients with renal transplant

Case No	Transplant Interval (month)	Gestational age (week)	Birthweight (g)	Apgar score (1-minute)	Apgar score (5-minute)	Adverse outcome
1	84	35	2100	7	9	
2	84	24	595	3	6	PPROM
3	72	36	2350	8	10	
4	72	38	2300	8	10	
5	108	33	1500	2	6	IUGR

PPROM: preterm premature rupture of membranes, IUGR: intrauterine growth restriction

with a functioning renal transplant becomes pregnant. Of the conceptions, 40% do not go beyond the initial trimester because of spontaneous or therapeutic abortion. More than 90% of pregnancies that continue past the first trimester end successfully (1).

Case Series Report

Table 1 summarizes the perinatal outcome. Table 2 summarizes the clinical characteristics of the patients.

Case 1

Twenty-year-old patient with renal transplant of seven years was admitted to our clinic with 35 weeks of pregnancy. Her blood pressure was 190/100 mm Hg at admission. She had been receiving the combination of prednisone, cyclosporine A and azathioprine as the immunosuppressant therapy. Laboratory evaluation revealed serum creatinine concentration of 1.69 mg/dl. She delivered a male infant of 2100 g by cesarean section due to cervical dystosia with the 1-and 5-minute Apgar scores of 7 and 9, respectively. The mother's postoperative course was uneventful. The newborn had no medical problem.

Case 2

Thirty two-year-old patient with renal transplant of seven years was admitted to our clinic with 24 weeks of pregnancy and premature preterm rupture of membranes. She had been receiving the combination of prednisone and cyclosporine A as the immunosuppressant therapy. Her blood pressure was 140/90 mm Hg at admission. Laboratory evaluation revealed serum creatinine concentration of 2.03 mg/dl. She delivered a female fetus of 595 g vaginally with the 1-and 5-minute Apgar scores of 3 and 6, respectively. The mother experienced acute graft rejection after the delivery. The newborn received ventilatory support and antibiotherapy because of the development of sepsis and died six days later.

Case 3

Twenty four-year-old patient with renal transplant of six years was admitted to our clinic with 36 weeks of pregnancy. Her blood pressure was 140/100 mm Hg at admission. She had been receiving the combination of pred-

Table 2. The clinical characteristics of the renal transplant patients

Case No	Creatinine level (mg/dL)	Graft rejection	Blood pressure (mm Hg)	Age
1	1,69	No	190/100	20
2	2,03	Yes	140/90	32
3	2,38	No	140/100	24
4	1,75	No	140/100	24
5	1,78	No	140/90	31

nisone, cyclosporine A and azathioprine as the immunosuppressant therapy. Laboratory evaluation revealed serum creatinine concentration of 2.38 mg/dl. She was transfused two units of erythrocyte suspension because of the initial hemoglobin level of 8.4 g/dL. She delivered a female infant of 2350 g by cesarean section due to cephalopelvic disproportion with the 1-and 5-minute Apgar scores of 8 and 10, respectively. The mother's postoperative course was uneventful. The newborn had no medical problem.

Case 4

Twenty four-year-old patient with renal transplant of six years was admitted to our clinic with 38 weeks of pregnancy. She had been receiving the combination of cyclosporine A and azathioprine as the immunosuppressant therapy and methyldopa as the antihypertensive therapy. Her blood pressure was 140/100 mm Hg at admission. Laboratory evaluation revealed serum creatinine concentration of 1.75 mg/dl. She was transfused two units of erythrocyte suspension because of the initial hemoglobin level of 7.9 g/dL. She delivered a female infant of 2300 g by cesarean section due to breech presentation with the 1- and 5-minute Apgar scores of 8 and 10, respectively. The mother's postoperative course was uneventful. The newborn had no medical problem.

Case 5

Thirty one-year-old patient with renal transplant of nine years was admitted to our clinic with 33 weeks of pregnancy. She had been receiving the combination of cyclosporine A and azathioprine as the immunosuppressant

therapy and nifedipine as the antihypertensive therapy. Her blood pressure was 140/90 mm Hg at admission. Laboratory evaluation revealed serum creatinine concentration of 1.78 mg/dl. She was transfused three units of erythrocyte suspension because of the initial hemoglobin level of 8.0 g/dL. Intrauterine growth restriction was detected by the transabdominal sonographic examination. She delivered a female infant of 1500 g by cesarean section due to intrauterine asphyxia with the 1-and 5- minute Apgar scores of 2 and 6, respectively. Her postoperative course was uneventful. The newborn had minimal respiratory distress and received prophylactic antibiotherapy; otherwise, she experienced no significant medical problem.

Discussion

Davison (1) reviewed the outcomes in 3382 pregnancies in 2409 women, 80% of whom had had cadaveric transplants. Most were treated with azathioprine and prednisone alone. The incidence of spontaneous and therapeutic abortion in the series by Davison was 35 percent. Of the pregnancies that continued beyond the first trimester, over 90 percent had a successful outcome. The glomerular filtration rate in these women usually increases in proportion to that seen in normal women. Although proteinuria developed in 40 percent of these women, it was not significant in the absence of hypertension. Preeclampsia developed in 30 percent and signs of kidney rejection were observed in about 10 percent. Without renal biopsy, however, ejection may be difficult to distinguish from acute pyelonephritis, recurrent glomerulopathy, or severe preeclampsia. Serious infections, most likely due to immunosuppressive therapy, complicated some pregnancies. Urinary infections were diagnosed in 40 percent and the incidence of viral infections was increased. Premature rupture of membranes and preterm labor were common, and about half of live-born infants were delivered preterm. Fetal growth restriction averaged 20 percent. Although respiratory distress syndrome was common among the preterm infants, it was seldom fatal. Fetal malformations were not increased. The newborns, as well as the mothers, were at increased risk of infection because of maternal immunosuppressive therapy.

Renal transplant patients should have good general health without severe hypertension for at least 2 years after transplantation, because graft rejection is more common during this period. There should be no evidence of graft rejection or persistent proteinuria. Renal functions should be stable with serum creatinine of 2 mg/dl or less. Even so, the effects of pregnancy are unpredictable and not necessarily related to previous rejection episodes, lack of problems in previous pregnancies, or human leukocyte-antigen typing. If stable, prednisone dosage should be maintained at 15 mg/day or less, and azathioprine at 2 mg/day or less. Azathioprine hepatotoxicity with severe jaundice may develop during pregnancy. A reduction in dosage is likely to improve hepatic function. Although not considered teratogenic, azathioprine is listed in category D. Safe doses of cyclosporine have not yet been established because of limited clinical experience, but 5 mg/kg/day or less is quoted anecdotally (2).

Cyclosporine A is given routinely in renal transplant recipients, but its use raises special concerns. Specifially, it decreases the glomerular filtration rate and also may cause hypertension. In nonpregnant patients, cyclosporine may be associated with renal funstion loss, hyperkalemia, hyperuricemia, hypertension and rarely, a hemolytic-uremic type syndrome (3). Data on the effects of cyclosporine A given during pregnancy are just emerging. Armenti et al (4), in observations from a national transplant registry of 154 births of exposed women, reported an excess of low-birthweight infants, although fetal outcomes were generally satisfactory. In a review of 54 pregnancies in 37 allograft recipients, Haugen et al (5) reported an increased frequency of spontaneous and induced abortions, as well as an increase in preterm deliveries. Concern persists over the posibility of late effects in the offspring subjected to immunosuppressive therapy in utero. These include malignancy, germ cell dysfunction, and malformations in the offspring's children. Although pregnancy-induced renal hyperfiltration theoretically may impair long-term graft survival, Sturgiss et al (6) found no evidence for this in a case-controlled study of 34 allograft recipients followed for a mean of 15 years.

Patients must be monitored as high-risk cases. Management requires attention to serial assessment of renal function, diagnosis and treatment of rejection, blood pressure control, early diagnosis or prevention of anemia, treatment of any infection, and meticulous assessment of fetal well-being. While there are risks to mother and fetus, there has not been an increased incidence of malformations noted in the newborn of the transplant recipient. It is essential that there is closely coordinated care that involves the transplant team and the obstetrician in order to obtain a favorable outcome. Immunosuppression should be maintaned at appropriate levels during pregnancy. At present, most immunosuppresive maintenance regimens include combination therapy, usually cyclosporine A or tacrolimus based. Most female transplant recipients will be receiving maintenance therapy prior to and during pregnancy. For some agents, including monoclonal antibodies and mycophenolate mofetil, there is either no animal reproductive information or there are concerns about reproductive safety. The optimal transplant recipient can be defined by pre-conception criteria which include good transplant graft function, no evidence of rejection, minimum 1 to 2 years post-transplant and no or well-controlled hypertension. For these women pregnancy generally proceeds without significant adverse effects on mother and child. It is of note that the epidemiological data available to date on azathioprine-based regimens are favorable in the setting of a category D agent (7).

Kozlowska-Boszko et al (8) investigated the impact of pregnancy on graft survival. Serum creatinine concentration and daily urine protein loss in 33 pregnant renal allograft recipients treated with prednisone and azathioprine and cyclosporine A were studied 6 months before, during and 6 months following delivery. As measured only by serum creatinine concentration graft function was stable in all patients. Significant rise in serum creatinine concentration following pregnancy was found in 6 of 33 patients. This unstable group was compared with 27 patients with stable despite pregnancy graft function. Proteinuria, but not serum creatinine concentration differentiated groups prior to pregnancy. The estimation of proteinuria prior to conception seems to be more potent parameter to predict kidney graft deterioration following pregnancy than serum creatinine concentration alone.

It is clear that women with a renal transplant can have a successful pregnancy but there are definite risks for both mother and fetus. The most important risk for the mother is a significant reduction in allograft function during pregnancy and the most important risks for the fetus are prematurity and intrauterine growth restriction. In the retrospective study of Cararach et al (9) among the 58 pregnancies of renal transplant patients that reached >28 weeks gestation, preterm birth occurred in 28 (48%) and intrauterine growth restriction occurred in 17 (29%). Among 48 women with normal renal function before pregnancy, the perinatal mortality rate was 142 per 1000, the miscarriage rate was 22% and in six of these women (33%) renal function deteriorated after pregnancy. Impairment of renal function as most common in women with hypertension during pregnancy or with rejection episodes during the year before conception. Muirhead et al (10) also reported 22 pregnancies in renal transplant patients 14 of them ending prematurely prior to 37 weeks. Hypertension complicated 10 pregnancies. Ten of 23 offspring were below the 10th percentile for weight. The mean birth weight and gestational age of children born to mothers taking cyclosporine A were lower than those in azathioprine treated mothers but these differences were not statistically significant.

With more renal allograft recipients becoming pregnant, it is important to identify factors influencing perinatal outcome. Sturgiss et al (11) analyzed gestational renal response and acute or chronic hypertension in relation to perinatal outcome for 22 pregnancies that continued beyond 28 weeks' gestation in 17 allograft recipients. Perinatal outcome was adverse in ten pregnancies: five stillbirths, four growth-restricted infants, and one neonatal death, whereas 12 pregnancies had satisfactory perinatal outcome. Early-pregnancy increments and late-pregnancy decrements in renal function were identical in both groups. Mean arterial pressure was significantly higher at 16-28 weeks in women having adverse outcomes. Hypertension (mean arterial pressure above 107 mm Hg) occurred in 16 pregnancies (73%); it appeared before 28 weeks in seven and was invariably associated with adverse outcome. Hypertension appeared after 28 weeks in nine women and was associated with adverse outcome in only two cases. Five of six pregnancies in women who were on pre-pregnancy antihypertensive therapy ended in adverse outcome.

In conclusion, renal function was identical in pregnancies having adverse or satisfactory perinatal outcome, whereas hypertension before or during early pregnancy, albeit apparently satisfactorily controlled, appeared to be associated with adverse perinatal outcome. This may be due to the covert microvascular changes associated with chronic hypertension compromising gestational cardiovascular adaptations, including the ability to develop and maintain an adequate uteroplacental circulation. The incidence of adverse outcome was higher than would be expected in a population of pregnant women with a similar level of essential hypertension but without renal transplant, indicating that renal transplant recipients are or have been susceptible to systemic and injurious effects of hypertension.

In our study we observed hypertension in all of the five patients. Preterm premature rupture of membranes was observed in a patient with 24 weeks of pregnancy resulting in neonatal death after vaginal delivery. The same patient also experienced acute graft rejection. Intrauterine growth restriction was observed in a patient with 33 gestational weeks of pregnancy. Fetal malformations were not observed. Eighty percent (4/5) of the patients tolerated the pregnancy well without any graft dysfunction.

Close surveillance is necessary for the pregnant patients with renal transplantation. Covert bacteriuria must be treated, and if recurrent, suppressive treatment for the remainder of pregnancy is given. Serial serum hepatic enzyme concentrations and blood counts should be monitored for toxic effects of azathioprine. Gestational diabetes is more common if corticosteroids are taken, thus, glucose tolerance testing is done at about 26 weeks. Renal function is monitored, at first with serum creatinine determinations, but if abnormal, determination of glomerular filtration rate is preferable. Hou (12) suggests that a decline of less than 30% in the glomerular filtration rate during the third trimester is normal and need not to be evaluated aggressively. Moreover, renal function in women with adverse perinatal outcomes was not different than in women with good outcomes (11).

Throughout pregnancy, renal transplant patients should be carefully monitored for development or worsening of underlying hypertension, and especially superimposed preeclampsia. Management of hypertension during pregnancy is the same as for non-transplanted patients. The kidney dilates minimally to moderately as do normal kidneys (13). Fetal growth should be monitored because of the significantly increased risk of fetal growth restriction and preterm delivery. Although cesarean delivery is reserved for obstetrical indications, occasionally the transplanted kidney will obstruct labor. In our series we performed cesarean section in four out of five patients because of obstetrical indications.

One factor affecting pregnancy outcome in kidney recipients is the length of time from transplantation to conception or transplant interval. It has been recommended that patients wait at least two years posttransplantation to conceive, as transplant intervals of shorter duration have had less favorable outcomes. Gaughen et al (14) showed that pregnancy outcomes in cyclosporine-treated recipients with transplant intervals greater than five years are favorable for the newborn, recipient, and graft. In our study the mean transplant interval was greater than five years in all of the patients.

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