

Pregnancy after renal transplantation: five cases

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Abstract

Objective: With the increasing rates of successful renal transplantations, the desire to get pregnant has come into prominence in fertile women. After renal transplantation, renal and endocrine functions return to normal values rapidly and ovulatory menstrual cycles begin; patients planning pregnancy can have a healthy pregnancy and live birth. In this study, we aimed to discuss pregnancies with renal transplantation followed up in our clinic.

Methods: Gestational follow-ups and perinatal outcomes of 5 patients who underwent renal transplantation due to end-stage renal failure and then got pregnant and delivered within the last two years at Dr. Lütfi Kırdar Kartal Training and Research Hospital were evaluated.

Results: Of the cases, mean age was 28.4±3.04 (range: 25 to 32) years, gravida was 2 (range 1 to 3), parity was 0 (range: 0 to 1), abortion was 0 (range: 0 to 2), mean week of delivery was 36.2±1.09 (range: 35 to 38) weeks, and mean birth weight was 2470±519.13 (range: 2000 to 3280) g. Of the patients, protein amount in 24-h urine was 3174.6±5458.41 (range: 94 to 12,783) mg, and the period between renal transplantation procedure and pregnancy was 4.7±1.92 (range: 2.5 to 7) years. Four of the cases were delivered due to obstetric reasons and one of them was delivered by C-section with the advice of nephrology department. No congenital anomaly was found in any of the baby of the cases.

Conclusion: There are many risks for patients with renal transplantation in terms of maternal and fetal aspects. Resulting pregnancy successfully depends on keeping the doses of immunosuppressive drugs at a level both protecting graft functions and not harming fetus, and the follow-up and treatment of gestational complications. Therefore, a multidisciplinary approach consisting of nephrology, obstetrics and neonatology specialists should be recommended for the follow-up of patients.

Keywords: Pregnancy, chronic renal failure, renal transplantation.

Özet: Renal transplantasyon sonrası gebelik: Beş olgu

Amaç: Fertil yaştaki kadın hastalarda, başarılı böbrek transplantasyonlarının artması sonucu gebelik istekleri ön plana çıkmıştır. Renal transplantasyon sonrası birçok kadında renal ve endokrin fonksiyonlar hızla normale dönerek ovulatuvar menstrüel sikluslar başlamakta, gebelik istemi bulunan hastalar sağlıklı bir gebelik ve canlı doğum elde edebilmektedir. Bu çalışmada kliniğimizde takip edilen renal transplantasyonlu gebelikleri tartışmayı amaçladık.

Yöntem: Dr. Lütfi Kırdar Kartal Eğitim ve Araştırma Hastanesi'nde, son dönem böbrek yetersizliği sebebiyle renal transplantasyon yapıp, son 2 yıl içerisinde gebelik elde edip doğum yapmış 5 hastanın gebelik takipleri ve perinatal sonuçları değerlendirildi.

Bulgular: Olguların ortalama yaşı 28.4±3.04 (aralık: 25–32), gravida 2 (aralık: 1–3), parite 0 (aralık: 0–1), abort 0 (aralık: 0–2), ortalama doğum haftası 36.2±1.09 (aralık: 35–38), ortalama doğum kilosu 2470±519.13 (aralık: 2000–3280) gram idi. Hastaların 24 saatlik idrarda protein miktarı 3174.6±5458.41 (aralık: 94–12.783) mg, renal transplantasyonları ile gebelik arası geçen süre 4.7±1.92 (aralık: 2.5–7) yıl bulundu. Olguların dördü obstetrik sebeplerle, biri ise nefroloji önerisiyle sezaryen ile doğurtuldu. Hastaların hiçbirinin bebeğinde doğumsal anomali saptanmadı.

Sonuç: Renal transplantasyonlu hastalarda maternal ve fetal açıdan pek çok risk bulunmaktadır. Gebeliğin başarılı bir şekilde sonuçlanması; kullanılan immünsupresif ilaç dozlarının hem greft fonksiyonlarını koruyacak hem de fetüse zarar vermeyecek düzeyde tutulmasına, gebelik komplikasyonlarının takip ve tedavisine bağlıdır. Bu nedenle hastaların takibinde nefroloji, obstetrik ve neonatoloji uzmanlarını içeren multidisipliner yaklaşım önerilmelidir.

Anahtar sözcükler: Gebelik, kronik böbrek yetersizliği, renal transplantasyon.

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Introduction

While pregnancy in patients with renal transplantation had been considered as risky in the past years, it has become less fearsome due to the increase in transplantation success in recent years and gradually increasing experience with successful pregnancies. Pregnancy after renal transplantation was reported first in 1963. When the literature is reviewed, it is seen that there are some risks as well as positive outcomes of pregnancies after renal transplantation. In the recent years, mortality rates have been decreased depending on the developments in renal transplantation and the life quality of patients has been improved. Another result obtained is the desire of fertile women to get pregnant. Menstrual dysfunction, amenorrhea, anovulation and infertility develop in cases with chronic renal failure. These functions get back to normal after a successful renal transplantation and ovulation starts in such patients,^[1] and 5% of patients can get pregnant. It is reported that 40% of the pregnancies conceived after renal transplantation could not complete first trimester due to spontaneous or therapeutic reasons, and 90% of those who completed the first trimester delivered successfully.^[2]

Since ovulation may start within 1-2 months following the transplantation, consultation should be provided to patients about appropriate contraception methods and the contraception should be started as soon as possible. Although most of the pregnancies conceiving after renal transplantation end up with live birth, the complication risk increases in patients with gestational hypertension and high level of creatinine before pregnancy. The patients are recommended to have stable graft function before pregnancy (serum creatinine <1.5 mg/dl, proteinuria <500 mg/day). While successful pregnancy rate in patients having preconceptional serum creatinine level below 1.4 mg/dl is 96%, it decreases to 70–75% in patients with higher level of serum creatinine.^[3] It is considered that infection and acute rejection risks are higher in pregnancies conceived within first year after transplantation. It is also not recommended to get pregnant within first year due to the teratogenicity potential associated with high doses of immunosuppressive drugs and antiviral drugs taken for viral infection prophylaxis. However, it was seen in the literature that there was no significant increase in the complications in the pregnancies conceived within first year.

Pregnancy rate within first three years in patients with renal transplantation is 3.3%, and live birth rate in those completing first trimester among these pregnan-

cies reaches up to 90%.^[2,4] While the most common problems during pregnancy are hypertension (62%), preeclampsia (29%) and infection (23%), the rates of prematurity, low birth weight, newborn complications and cesarean section vary between 41 and 55%.^[5]

Methods

Gestational follow-ups and perinatal outcomes of 5 patients who underwent renal transplantation due to end-stage renal failure and then got pregnant and delivered within the last two years at Dr. Lütfi Kırdar Kartal Training and Research Hospital were evaluated. The medical files of the cases who referred to the perinatology clinic, had the history of renal transplantation and live births were analyzed retrospectively. The ages, the date of transplantation, gravida, parity, abortion number, drugs they took and the doses, serum creatinine levels before and after pregnancy, complete blood counts, protein amounts in 24-h urine and hepatic function tests of the patients were investigated. It was found that all patients underwent anomaly screening. During the gestational follow-up of patients, presence of intrauterine growth retardation (IUGR) and any anomaly were measured ultrasonographically and noted. Complications of patients during pregnancy, delivery types and presence of complication during delivery were investigated. Apgar scores were checked with birth weights of babies.

The statistical analysis of the data was done by SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The lowest and highest values of mean, standard deviation and median were used in the descriptive statistics of the data. The data with constant and normal distribution were provided as mean±standard deviation, and the data without constant and normal distribution were provided as median (minimum-maximum).

Results

Demographic characteristics are given at **Table 1**. In the five patients who conceived after renal transplantation, mean age was 28.4±3.04 years, gravida was 2 (range: 1 to 3), and parity was 0 (range: 0 to 1). The patients had the transplantations approximately 4.7±1.92 (range: 2.5 to 7) years ago. The transplantation was done to three patients due to end-stage renal failure with unknown reason, one patient due to renal failure developed as a result of chronic hypertension, and one patient due to renal failure developed as a result of familial Mediterranean fever. All patients were taking azathio-

prine and tacrolimus. In addition these drugs, one patient was taking prednisolone 5 mg 1×1, one patient was taking nifedipine 30 mg 2×1 and prednisolone 5 mg 1×1, one patient was taking methyldopa 250 mg 2×1, prednisolone 5 mg 1×1 and vitamin D, and one patient was taking colchicines 1×1 mg. Two patients had pre-conception chronic hypertension. In the antenatal follow-up of all patients, tension arterials, blood biochemistry values and urine cultures were normal. The protein amount in 24-h urine of patients was 3174.6 ± 5458.41 g. First and second trimester screening tests of four patients were normal; amniocentesis was recommended to one patient when combined trisomy 21 risk was found as 1/160 in the first trimester screening test, but the patient did not accept. Oral glucose challenge test was performed on all patients. The values of four patients were normal while one patient was diagnosed as gestational diabetes. Blood glucose of the patient was regulated by diet. It was found in the follow-up visits of 4 pregnant women, women who had no fetal anomaly according to the ultrasonographic examination, that their ultrasonographic measurements were consistent with the week of gestation. Growth retardation was found in the

patient diagnosed as gestational diabetes. Premature rupture of membrane developed in one patient at 35 weeks of gestation. All patients underwent cesarean section. The reasons for cesarean section patients were breech presentation in primipara in one patient, increasing creatinine values in one patient, development of fetal distress during labor follow-up in one patient, grade-2 hydronephrosis development in transplanted kidney in one patient and upon the recommendation of nephrology department due to the pain description of the patient in that region, and identification of IUGR in one patient. Mean delivery week was 36.2 ± 1.09 (range: 35 to 38). Mean weight of newborns was 2470 ± 519.13 (range: 2000 to 3280) g, 1-minute Apgar score was 8 (range: 7 to 9), and 5-minute Apgar score was 9 (range: 8 to 10). With the recommendation of nephrology department, all patients were administered preop 100 mg prednisolone i.v., 80 mg i.v. prednisolone on postop first day, 40 mg i.v. prednisolone on postop second, third and fourth days, and 32 mg i.v. prednisolone on postop fifth day. Later on, patients continued with oral 5 mg tablet 1×1. Mean hospitalization period was 3 (range: 2 to 5) days. Congenital anomaly was not seen in any baby.

Table 1. Demographic data of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	31	25	32	28	26
Transplantation time (how many years ago)	6	2.5	5	3	7
Gravida	3	1	2	2	1
Parity	0	0	1	1	0
Abortion	2	0	0	0	0
Drugs taken	Azathioprine + tacrolimus	Tacrolimus + azathioprine + nifedipine + prednisolone	Azathioprine + tacrolimus + prednisolone	Azathioprine + tacrolimus + prednisolone + methyldopa	Azathioprine + tacrolimus + colchicines
Hypertension	-	+	-	+	-
Protein in 24-h urine (mg)	94	2450	306	240	12783
Complication	Premature rupture of membrane	Anemia, creatinine increase during pregnancy, hypertension	Anemia	Hypertension	Gestational diabetes, IUGR
Delivery type	Cesarean	Cesarean	Cesarean	Cesarean	Cesarean
Birth weight (g)	2070	2360	3280	2640	2000
Apgar score	7/8	8/9	8/9	9/10	8/9
Hospitalization (day)	2	3	2	5	2
Cesarean indication	Breech presentation in primipara	Creatinine increase	Fetal distress	Hydronephrosis	IUGR

IUGR: Intrauterine growth retardation

Discussion

In patients with end-stage renal failure, fertility decreases 10 times due to ovarian dysfunction, anovulation and libido loss. Renal and endocrine functions return to normal levels in many women within 1–2 months after successful renal transplantation and ovulatory cycles begin and it becomes possible to conceive. Thanks to the improved surgical techniques and immunosuppressive drugs, one out of 50 fertile women with functional kidney after transplantation conceives.^[5]

As pregnancy with transplanted kidney comes with some risks and ovulation may return immediately after transplantation, it is essential to provide contraception consultancy to patients during the first years in particular. Centers for Disease Control and Prevention (CDC) recommends contraceptive methods to the patients underwent solid organ transplantation whether being complicated (those with acute or chronic graft failure or rejection) or non-complicated. While hormonal contraceptive methods containing progesterone or barrier methods can be used safely in complicated group, hormonal contraceptives containing estrogen are not preferred. In non-complicated patient groups, all contraceptive methods can be preferred. In addition to contraception method, consultancy should also be provided about the most suitable pregnancy timing, maternal and fetal outcomes, effects of immunosuppressive drugs on fetus, risks on renal graft, and other medical problems. Most of the studies performed report that a stable pregnancy in renal transplantation does not cause any negative irreversible effect on graft functions.^[6] Graft loss rate in pregnant women undergoing immunosuppressive treatment was found as 8–11% within two years and no difference was observed between them and non-pregnant women.^[7] The risks for acute rejection and infection are generally higher in pregnancies conceived within one year after transplantation and potential teratogenicity is higher within first year due to high dose exposure to immunosuppressive drugs and antiviral drugs used for viral infection prophylaxis. Therefore pregnancy is not recommended preferably within first year. For pregnancy planning, it is recommended having sufficient and stable graft function (serum creatinine <1.5 mg/dl, proteinuria <500 mg/day), not having rejection history within last one year, providing stable dose of immunosuppressive treatment, and not having any additional disease which may affect pregnancy and graft function. It is likely to result in a pregnancy conceived after meeting these conditions in a positive way even if it is within 6–12 months after transplantation.

However, generally, it is advised to wait for 2 years after transplant for maternal and fetal well-being.^[3] Estimated pregnancy rate within first three years after renal transplantation is 3.3%, and 75–80% of these pregnancies result in live birth.^[4] The pregnancies of 40% of patients with renal transplantation who delivered in our clinic were conceived within 3 years after transplantation and 60% of them after 3 years.

Although the complication risk increases in patients with hypertension and high level of serum creatinine before pregnancy, most of these pregnancies result in live birth. While successful pregnancy rate in patients having preconceptional creatinine level below 1.4 mg/dl is 96%, it decreases to 70–75% in patients with higher levels of creatinine.^[8] In our case series, preconceptional serum creatinine levels were below 1.4 mg/dl in all patients.

Proteinuria may be seen in the third trimester as a result of physiological hyperfiltration during pregnancy; however, it returns to normal levels three months after the pregnancy. The presence of proteinuria during the early periods of pregnancy is the indicator of previous kidney damage and it is associated with the increase of renal dysfunction risk together with hypertension.

There is an increased risk in patients with renal transplantation during pregnancy, especially in terms of hypertension (53–68%), preeclampsia (27%), preterm labor (45.6%), premature rupture of membrane, low birth weight, IUGR and infection. All these risks are closely associated with renal functions. The rate of spontaneous abortion is 14.7% and therapeutic abortion rate is 4.9%, which are similar to general population.^[9] First preference should be alpha methyl dopa in patients developing hypertension due to its safety. Diabetes mellitus is seen in 9% of the patients with renal transplantation. Prednisolone and calcineurin inhibitor may cause it. These patients should be subjected to 50-g oral glucose challenge test at every trimester and 100-g glucose challenge should be done on those negative values. The immunosuppressive drugs taken come with increased infection risk. The most common ones are urinary infections and its incidence is 42%. Asymptomatic bacteriuria should be treated. Another problem in transplanted patients is the anemia developing due to the insufficient production of erythropoietin. Patients should be followed up with complete blood count every 2–4 weeks in terms of anemia. While the chronic hypertension in 40% of the patients in our case series was regulated with medical treatment, 40% of the patients developed anemia, 20% of the patients developed premature rupture

of membrane, 20% of the patients developed gestational diabetes, 20% of the patients developed creatinine increase during pregnancy, and 20% of the patients developed IUGR, but no pregnancy was resulted in poor prognosis in any case.

Pregnancies of transplanted patients should be followed up as high-risk pregnancies. In the follow up of pregnancies, urinary culture test every 4–6 weeks, hemoglobin level, renal and hepatic function tests, serum calcium and protein analysis in 24-h urine should be recommended as well as tension arterial follow up. In the admission, it would be appropriate to evaluate CMV status every trimester as well as the evaluation of HIV and hepatitis B serology. In case that no problem arises during pregnancy, it can be waited until spontaneous labor starts and vaginal labor is recommended. Transplanted kidney does not cause vaginal obstruction while vaginal labor does not have any negative impact on transplanted kidney. To prevent infection during labor, antibiotic prophylaxis should be applied in invasive procedures such as amniotomy and episiotomy or during c-section. Cesarean labor should only be recommended according to standard obstetric indications and the locations of allograft and ureter should be confirmed before the operation. The location of graft is significant in terms of both ureter and the proximity of vessel anastomoses to uterus. The evaluation done before cesarean may prevent both possible ureter and vein damages. In our case series, 3 patients delivered by cesarean for obstetric reasons and 2 patients for nephrologic reasons.

The drugs maintained after delivery pass into the breast milk. However, the postnatal outcomes of these drugs passing through lactation are not exactly known, the safety of lactation after delivery is unclear. Yet, there is no certain contraindication for lactation. American Pediatrics Academy supports mothers taking prednisolone to lactate while not recommending mothers to lactate when taking cyclosporine, and abstains on the lactation by mothers who take azathioprine and tacrolimus. There is no certain information about the amount of mycophenolate and sirolimus in breast milk. Sixty percent of our patients lactated.

It is required to maintain immunosuppressive drugs during pregnancy which are taken by patients. Although most of these drugs pass into the placenta, they are subject to first pass effect in fetal liver and they are usually at an insignificant level in fetal blood in terms of potential teratogenous effects.^[8] Immunosuppressive agents frequently used after renal transplantations are calcineurin

inhibitors (cyclosporine, tacrolimus), antiproliferative agents (azathioprine and mycophenolate), TOR (target of rapamycin) inhibitors (sirolimus and everolimus) and steroids. Congenital anomaly rate in pregnant women undergoing immunosuppressive treatment (except mycophenolate acid) is usually similar to the general population.^[7] The relationship was reported between mycophenolic acid exposure, of which pregnancy category is D, and anomalies such as hypoplastic nail, short fifth finger, and ear and face deformities.^[10,11] Since there is no sufficient information about the use of sirolimus, which is another agent, it is not recommended during pregnancy. In a study conducted for gestational complications, the group taking tacrolimus + azathioprine was compared with the group taking cyclosporine, and less increase in chronic hypertension, preeclampsia, anemia and urinary infection and increase in diabetes risk were found in the group taking tacrolimus + azathioprine.^[12] Four out of 5 patients in our case series were administered tacrolimus + azathioprine, and premature rupture of membrane in one patient, anemia in one patient, chronic hypertension in one patient and gestational diabetes as well as IUGR were developed. In another study performed, risk increases for neurocognitive disease and attention deficit disorder with hyperactivity were observed in babies subjected to immunosuppressive drugs during intrauterine period.^[7] Consequently, while cyclosporine, azathioprine and prednisolone are safe during pregnancy, mycophenolic acid and sirolimus should not be taken during pregnancy and it should be planned to cease taking them at least 6 weeks before pregnancy. Doses of the drugs decided to administer should be readjusted during pregnancy.

Conclusion

Although most of the pregnancies conceived with the rapid recovery of renal functions after renal transplantation result in live birth, patients should be followed up closely in terms of increasing complications. Since the pregnancy timing is associated with complications, the most appropriate time should be waited after transplantation and consultancy should be provided to families. Patients should switch to an appropriate immunosuppressive treatment before pregnancy. The pregnancy should be followed up by a multidisciplinary team consisting of obstetrician, nephrology specialist and newborn specialist. Minimizing the complications with close follow-up encourages parents who desire to have a baby.

Conflicts of Interest: No conflicts declared.

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