Successful Management of Pregnancy in Two Kidney Transplant Recipients

Böbrek Nakilli İki Olguda Başarılı Gebelik Yönetimi

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ABSTRACT Renal failure results in impaired reproductive function especially among women. One of the important benefits of kidney transplantation in women of reproductive age is to improve fertility owing to restoration of pituitary-ovarian function. Attained fertility has resulted in high number of pregnancies. However, the long-term effects of pregnancy on both graft and child is debated issue. Of special concern are the new immunosuppressive drugs where data have shown eventful outcomes in the newborn. This article describes successful delivery in two patients who became pregnant after 5, and 6 years posttransplantation, respectively. They both received calcineurine-based regimens, and completed the pregnancies with well functioning grafts and healthy newborns who have presented well neurological and physical development to date.

Key Words: Pregnancy; tacrolimus; kidney transplantation; cyclosporine

ÖZET Böbrek yetmezliği özellikle kadınlarda sıklıkla üreme işlevlerinde bozulmaya neden olmaktadır. Böbrek naklinin önemli yararlarından biri de hipofiz-over fonksiyonlarının düzelmesine bağlı olarak fertilitenin iyileşmesidir. Geri kazanılan fertilite sonucunda gebelik sayısında artma olmaktadır. Ancak gebeliğin nakil böbrek ve fetus üzerine uzun dönem etkileri hala tartışmalı bir konudur. Önemli bir sorun da yenidoğanda önemli sonlanımlara neden olduğuna dair verilerin bildirildiği yeni immünosüpresiflerin kullanımıdır. Bu makalede nakil sonrası sırasıyla beşinci ve altıncı yıllarında gebelik gelişen böbrek nakilli iki olguda başarılı sonlanım sunulmuştur. Olguların her ikisi de kalsinörin temelli protokoller ile tedavi edilmiştir. Gebelikler nakil böbrek işlevlerinin korunması ve sağlıklı fetus ile tamamlanmıştır; halen fetal nörolojik ve fiziksel gelişimler iyi sürdürülmektedir.

Anahtar Kelimeler: Gebelik; takrolimus; böbrek transplantasyonu; siklosporin

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The first successful pregnancy was reported by Murray and collegues in a 21-year-old woman who received a kidney transplant from her identical twin sister.[1] As the patient was not on immunosuppression, the only concern was compression of the renal vessels and kidney by the enlarging uterus. Finally a normal male infant was delivered by cesarean section without any adverse effect on allograft function. However in cases of transplantations from living-related other than identical twin donor or deceased donors immunosuppressive medications are the mainstay of the medical management. Subsequently, first report of pregnancy in a kidney recipient on immunosuppression of azathioprine (AZA) and prednisone

(Pred) came into scene in 1967.[2] Thereafter the experiences with pregnancies after transplantation in the setting of immunosuppression increasingly accumulated. About 5% of all women of reproductive age with a functioning kidney transplant will become pregnant.[3] In order to prevent allograft dysfunction maintenance therapy to achieve sufficient immunosuppression, while avoiding the toxicity to growing fetus, should continue throughout pregnancy. Here we presented two cases on immunosuppression with a functioning graft, in whom we encouraged pregnancies.

CASE REPORT

CASE 1

A 32-year-old female underwent kidney transplantation in 2002 from a deceased donor. She received induction by anti-thymocyte globulin (ATG), and cyclosporine (CsA) was commenced in a dose of 5 mg/kg/d on 6th postoperative day when creatinine level was 1.7 mg/dL. She was discharged on the 19th postoperative day with CsA, mycophenolate mofetil (MMF), and Pred regimen with serum creatinine of 1.4 mg/dL. During follow-up her serum creatinine levels remained stable between 1.2 to 1.5 mg/dL until 2005 when serum creatinine level increased to 1.67 mg/dL. We made allograft biopsy in order to diagnose rejection. The pathological diagnosis was compatible with acute rejection. Pulse methylprednisolone therapy in a dose of 500 mg/d for 3 days was started. The patient had serum creatinine levels ranging between 1.3 to 1.6 mg/dL thereafter. As she decided to have pregnancy in 2007 we discontinued MMF, and instituted AZA (100 mg/d in two divided doses) instead before six months of conception. Throughout pregnancy she remained normotensive with stable creatinine levels, and without any proteinuria. She was maintained on cyclosporine-based immunosuppression without any complications (creatinine, 1.3 mg/dL at last follow-up, and no proteinuria). There were no signs of graft rejection. Fetal ultrasonographic evaluations were also normal. During the 37th gestational week the patient underwent a cesarean section, giving live-birth to a 2909-g healthy male infant without any malformations. The renal function of the patient did not deteriorate following postpartum. She has still had a moderately well functioning graft with last creatinine level of 1.4 mg/dL.

CASE 2

A 28-year-old female with end stage renal disease due to vesicoureteral reflux underwent kidney transplantation from living-related donor (her father) in 2003. She was on hemodialysis therapy for about thirteen months before transplantation. She was immunosuppressed with tacrolimus (TAC) 2mg/d administered in two divided doses, AZA 100 mg/g in two divided doses, and Pred. She was discharged with serum creatinine level of 1.1 mg/dL. After 6 years posttransplantation she decided to have pregnancy. She had well functioning graft without any rejection episode during follow-up. She was maintained on the same regimen through pregnancy with serum creatinine levels ranging between 0.9 to 1.1 mg/dL. An ultrasound showed normal fetal anatomy in the 30th and 34th gestational weeks. At 35th gestational week her blood pressure was 140/95 mmHg , and on physical examination she had 2+ pretibial edema. She was admitted to the hospital , and methyldopa in a dose of 250 mg three times daily was initiated as an antihypertensive medication. She had no proteinuria or graft dysfunction. During 38th gestational week she underwent a cesarean section, giving live birth to a 3650-g, healthy male baby, without any birth defects. She has stable renal function from delivery till now (creatinine, 1.1 mg/dL at last follow-up) with a healthy child.

DISCUSSION

Renal failure is generally associated with impaired fertility in women of reproductive age, and kidney transplantation enables restoration of pituitary-ovarian function, and hence fertility after about six months of transplantation. The first successful pregnancy outcome reported in the literature was a woman transplanted from her twin sister in 1958, by Murray and collegues.[1] That was the case without on an immunosuppressive schedule. Subsequently the first report in 1967 pointed out the

pregnancy in the setting of immunosuppression with AZA and Pred.[2] Thereafter increasingly accumulated data has been available regarding pregnancies after both renal and other transplantations. In renal transplantations about 1 in 5 pregnancies will end in spontaneous abortion in the first, trimester, but those that go beyond this period , at least 90% will end successfully.[3]

Pregnant women with transplanted organ have some issues concerned as risks to the health of the mother for long term , to allograft , and to fetus in terms of teratogenicity. Allograft loss may result in retransplantation or even death especially in heart, lung , and liver recipients. Therefore female recipients contemplating pregnancy should be counseled for long-term maternal, graft , and fetal survival.[2,4] Although pregnancies in a kidney recipient may be complicated by preterm labor (30 to 50 %), preeclampsia (30 to 37 %), and intrauterine growth retardation (IUGR, 20 to 33%), the pregnancy does not appear to affect rate of rejection unless preconception serum creatinine is more than 1.5 mg/dL and urinary protein excretion more than 500 mg/d.[4,5] Because the level of immunosuppression is kept high in the 3 months following transplantation, to avoid fetal exposure to high levels of immunosuppressants, recipients are usually advised to delay pregnancy for at least 1 to 2 years by the time they will be on maintenance immunosuppression.[5,6] As also reported recently by Levidiotis and collegues[3] a safe interval between transplantation and pregnancy is 1 to 4 yr, with a live birth in 72.7 % of cases. This status is compatible with both cases presented here.

Generally used maintenance regimens include a glucocorticoid (e.g prednisone), with an antimetabolite (AZA or MMF), and/or calcineurin inhibitor (TAC or CsA).[7] The fetus is inevitably exposed to these medications during development. Short-acting nonfluorinated corticosteroids (prednisone and methylprednisolone) are metabolized by placental 11-beta-hydroxysteroid dehydrogenase so that only low levels are detected in the fetal circulation. On the other hand, the fluorinated steroids (betamethasone and dexamethasone) cross the placenta in their active form, and reach high concentrations in the fetal circulation. The most commonly reported fetal congenital malformation associated with the use of glucocorticoids during pregnancy is cleft palate.[6] AZA and MMF are antimetabolites used as a component of maintenance immunosuppression. Although most of the studies suggests that AZA is not converted to its teratogenic metabolite, 6-mercaptopurine, by the placenta which serves as a relative barrier, cases of sporadic fetal malformations (e.g hypospadias and preaxial polydactyly) have been reported.[8] However, AZA is still an acceptable drug in transplant patients in pregnancy. In contrast to AZA , MMF and sirolimus are not recommended to be used during pregnancy by the European Best Practice Guidelines , as they may cause a number of structural fetal malformations.[2,6,9] On the other hand recent case report from Taiwan pointed out a successful delivery in a renal transplant pregnant on a sirolimus-based immunosuppression regimen.[10]

The National Transplantation Pregnancy Registry (NTPR)[11] was established to study the outcomes of pregnancies in transplant recipients in North America in 1991. All pregnancy outcomes including livebirths, stillbirths, spontaneous abortions, therapeutic abortions, and ectopic pregnancies were analyzed as well as long-term maternal and fetal effects, and allograft sequelae. According to this report, overall outcomes were not markedly different among CsA and TAC pregnancies with prevalence of fetal structural anomalies being nearly 4% to 5%. Animal data showing renal developmental anomalies in the offsprings of rabbits treated with CsA in pregnancy could not been validated in humans. And therefore CsA is still a component of immunosuppressive regimens. Of the 71 cases reported to NTPR in TAC group, 3 live born fetus, two of whom also exposed to MMF in pregnancy, were marked to have malformations.

The cases presented here were on generally accepted maintenance immnuosuppressive regimens in pregnancy (one CsA-based, the other TAC-based), so that we did not observe any fetal mal-

formations at birth as expected. But it should be kept in mind that long-term fetal follow-up is warranted since potential effects may not be apparent in the newborn and may not manifest until adulthood, as reported by Tendron-Franzin and collegues from France.[12] Any kidney recipient women in a reproductive age contemplating pregnancy should be well informed about the risks of pregnancy, and immunosupressions for both themselves and fetus as well.[13]

As a conclusion; the successful outcomes of these both pregnancies presented here can be attributed to ideal pre-fertilization renal function and maternal status regarding the time for pregnancies and exposure to low doses of medications, as well as to meticulous obstetrical follow-up.

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