

# Pregnancy Outcome in a Renal Transplant Recipient Treated with Tacrolimus

## GEBELİĞİNDE TACROLİMUS ALAN RENAL TRANSPLANTLI ANNE BEBEĞİ

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### Summary

**Objective:** We report here the outcome of a pregnancy in a woman with renal transplant maintained on tacrolimus and azathioprine.

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**Materials and Methods:** The male baby was delivered at a gestational age of 29 weeks, by emergency Cesarean section due to fetal distress and preterm premature rupture of membranes. Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. His birth weight was 1180 g. (25-50 percentile), head circumference was 26 cm. (10-25 percentile), and length was 36 cm. (25-50 percentile). His routine blood tests were all within the normal range, except a transient hyperkalemia detected on the first postnatal day and controlled two days later. He had a transient hyperkalemia on the first postnatal day. The echocardiogram, abdominal and cranial sonography were normal.

He also initially developed apnea and was treated with aminophylline that was tapered off on the postnatal 43<sup>rd</sup> day. He required two-day phototherapy for increased total bilirubin level (6.4 mg/dl) at the first day. He was discharged on 50<sup>th</sup> day.

**Conclusion:** The woman had kidney transplantation and received tacrolimus treatment during pregnancy and gave birth to healthy child. We would like to contribute to the available knowledge and experience in such conditions with our one case.

**Key Words:** Pregnancy, Tacrolimus, Renal transplantation

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### Özet

**Amaç:** Bu yazıda, gebeliğinde takrolimus ve azatiopürin tedavisi alan renal transplantlı bir annenin bebeği sunulmaktadır.

**Çalışmanın Yapıldığı Yer:** Adnan Menderes Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum AD, Çocuk Sağlığı ve Hastalıkları AD, Yenidoğan Yoğun Bakım Ünitesi, Aydın.

**Materyal ve Metod:** Erken, membran rüptürü ve fetal distress nedeniyle acil sekiyo-sezaryenle 29.gebelik haftasında doğurtulan erkek bebeğin, birinci ve beşinci dakika Apgar skorları sırasıyla 7 ve 8 idi. Doğum ağırlığı 1180 gr. (25-50 persantil), baş çevresi 26 cm. (10-25 persantil) ve boyu 36 cm. (25-50 persantil) ölçüldü. Bebeğin laboratuvar tetkiklerinde; kan biyokimyası, postnatal ilk gün ortaya çıkan, iki gün devam eden hiperpotasemisi dışında normal sınırlardaydı. Ekokardiogramı, abdominal ve kranial ultrasonografik incelemeleri normal bulundu.

Klinik izleminde, yaşamın ilk günlerinde gelişen, pre-matürite oluşundan kaynaklanan apneleri aminofilin tedavisine cevap verdi. İlk 24 saat de 6,4 mg/dl'ye ulaşan total bilirubin düzeyi nedeniyle, olguya iki gün süreyle fototerapi uygulandı. Doğum sonrası 50.günde olgu sağlıklı olarak taburcu edildi.

**Sonuç:** Bir olguya, böbrek nakli yapılmış ve gebeliğinde tacrolimus tedavisi alan annelerin de, sağlıklı çocuk sahibi olabileceklerine ait mevcut bilgilere katkıda bulunmak istedik.

**Anahtar Kelimeler :** Gebelik, Takrolimus, Renal transplantasyon

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Childbearing is important to women with renal disease, but pregnancy has generally been regarded as having very high risk for them. Patients with chronic renal insufficiency and end-stage renal disease, including dialysis patients and transplant recipients can usually expect pregnancy to result in a surviving infant. The frequency of

conception is decreased in women with renal insufficiency and markedly decreased in dialysis patients ranging from 1.4% per year in Saudi Arabia to 0.5% in the United States. Fertility however, is restored in women with renal transplants, and pregnancy is common, occurring in 12% of those within childbearing age in one series (1). The per-

centage of pregnancies resulting in surviving infants in women with renal insufficiency and transplant recipients ranges from 70% to 100% (2).

Exposure to immunosuppressive drugs, including prednisone, azathioprine, cyclosporine, and tacrolimus, has not been associated with an increase in congenital anomalies. All groups have an increased risk for prematurity and intrauterine growth retardation (2).

Tacrolimus is used as a therapeutic alternative to cyclosporine. Therefore it represents a cornerstone of immunosuppressive therapy in organ transplant recipients. Cyclosporine has higher incidence of significant side effects including hypertension, hypercholesterolaemia, hirsutism and gingival hyperplasia, while tacrolimus has a higher incidence of diabetes mellitus, some types of neurotoxicity (tremor, paraesthesia), diarrhea and alopecia (3).

Data on tacrolimus administration during pregnancy are still limited. Tacrolimus is known to cross the placenta. Consequently, neonatal hyperkalemia and renal dysfunction have been observed in association with the use of tacrolimus during pregnancy (2, 4).

There have been numerous publications describing pregnancies in transplanted patients who received cyclosporine, but the data on the outcome of pregnancy in those using tacrolimus are scarce. We report here the outcome of pregnancy in a woman with a renal transplant maintained on tacrolimus and azathioprine.

### Case Report

The mother was 29-year-old female and had her first pregnancy. She had received kidney transplant from her mother. Immunosuppressive agents, at that time were prednisone, cyclosporine, and azathioprine. The mother was treated with isradipine and atenolol for her hypertension after transplantation. There was no history of graft rejection episode. Her treatment was converted from cyclosporine to tacrolimus 5 years after transplantation. She was taking 0.1 mg / kg / day tacrolimus, 2mg / kg / day azathioprine and metyldopa at the time of delivery. During peripartum period, her white blood cell count was 12700/mm<sup>3</sup>, red blood cell count was 4 000 000 / mm<sup>3</sup> and platelet count was 252 000/mm<sup>3</sup>. Her serum BUN and creatinin levels were 19 mg / dl and 1.4 mg / dl, respectively.

The male baby was delivered at a gestational age of 29 weeks, by emergency Cesarean section due to fetal distress and preterm premature rupture of membranes. Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. On the physical examination, his birth weight was 1180 g. (25 - 50 percentile), head circumference was 26 cm. (10 - 25 percentile), and length was 36 cm. (25 - 50 percentile). He did not present any malformations. He was transferred

to the neonatal intensive care unit for close monitoring. He had no evident respiratory distress and was comfortable on room air with pulse oximetry showing saturation level of >95%. His chest X ray was normal.

His routine blood tests were all within the normal range, except a transient hyperkalemia detected on the first postnatal day and controlled two days later. Echocardiogram, abdominal and cranial sonography were also normal.

Ampicillin (100 mg/kg/day) and amikacine (18 mg/kg/36h) were administered for preterm premature rupture of membranes and the administration was stopped as soon as negative culture results were obtained. The infant was never breastfed.

Aminophylline was started to treat his apnea attacks and was tapered off at postnatal 43<sup>rd</sup> day. He required phototherapy for his increased total bilirubin level of 6.4 mg/dl on first of life. He was discharged when he was 50-day-old.

### Discussion

According to the Food and Drug Administration (USA), the current pregnancy risk categories for immunosuppressants are B (no evidence of risk in humans) for corticosteroids; category C (risk cannot be ruled out) for cyclosporine, mycophenolate mofetil, tacrolimus, and rapamycin; and category D (positive evidence of risk) for azathioprine. The remaining categories are A (controlled studies: no risk) and X (contraindicated).

Prednisolone crosses the placenta. Adrenal insufficiency and thymic hypoplasia have occasionally been described receiving prednisolone in the infants of transplant recipients receiving prednisolone (1). The mother of our case did not have prednisolone during pregnancy.

Azathioprine crosses the placenta readily, but to be active, it must be converted to

6-mercaptopurine. The immature fetal liver lacks the enzyme inosinate pyrophosphorylase, needed for conversion, and the fetus is relatively protected from the effects of the drug. However, in high doses, azathioprine is teratogenic in animals (1).

Limited immunologic and other abnormalities have occurred in a few infants born of renal transplant recipients on azathioprine (5, 6). Azathioprine has been associated with a dose - related myelosuppression in fetus, but leucopenia is not usually a problem in neonate if the maternal white blood count is maintained at greater than 7,500/μL (5).

Transplant recipients are at risk for infections that have implications for the fetus, including cytomegalovirus, herpes simplex, and toxoplasmosis (1).

White blood cells count, red blood cells count and platelet count of our patient were also within the normal range and there was no finding of infection during postnatal period.

Williamson and Karp (6) described an infant born with preaxial polydactyly whose mother received azathioprine and prednisone during pregnancy. The physical examination of our patient was normal.

Cyclosporine has not been associated with an increase in congenital anomalies but can cause intrauterine growth retardation and low birth weight (1,7). The frequencies of low birth weight in infants born to women receiving only azathioprine and prednisone are significantly less than the frequencies in the group of women who were also receiving cyclosporine (1).

Picaud et al. (8) reported 23 women who had undergone renal transplantation and given birth to 26 infants. In this study, immunosuppressive treatment consisted of azathioprine, and steroids in 20 cases, steroids and cyclosporine in one case, and azathioprine, steroids and cyclosporine in 5 cases. Average gestational age at birth was 35 weeks and average birth weight was 2330 g. They found that the most frequent neonatal pathological condition was respiratory distress, related to prematurity.

Successful pregnancies in kidney recipients with tacrolimus treated have been reported. The first published reports of babies born to tacrolimus-treated patient were in 1993 from Pittsburg in USA and from Hannover in Germany (8), followed by Armenti et al. (3) who presented data on cohorts of 22 pregnancies in 19 kidney recipients.

Pergola et al. (7) reported characteristics of transplanted cases treated with steroid, tacrolimus and mycophenolate mofetil during pregnancy. Infant complications were prematurity, hypoplastic fingers and toenails, bilaterally shortened fifth fingers, apnea bradycardia with feeds and aberrant blood vessel between trachea and esophagus. In our case, the baby had no such abnormalities.

In one series of nine pregnancies in women receiving tacrolimus, hyperkalemia was reported in five out of nine infants, and anuria in one for 36 hours (4).

Kainz A et al. (9) reported 100 pregnancies from 84 mothers who received tacrolimus systemically. Of 100 pregnancies, 71 have been progressed to delivery. Mean gestation period have been 35 weeks with 59% deliveries being premature. Similar to our case, birth weight has been

found appropriate for gestational age in 90% of the cases. They reported that most common complications in the neonates have been hypoxia, hyperkalemia, and renal dysfunction. Four neonates presented malformations with an incidence of 5.6% of live born infants. However, the ratio reported for the nontransplant population is 3% (2).

A case report has attributed the development of cardiomyopathy in twins to an adverse effect of tacrolimus (10). An echocardiogram of presented case revealed normal intracardiac anatomy.

In conclusion, considering known maternal and fetal risk such as congenital malformations and predisposition to infections this infant of kidney transplanted mother treated with tacrolimus and azathioprine during pregnancy had no severe problem except prematurity and a transient hyperkalemia. This case adds one more example to that favorable outcome of pregnancies under tacrolimus therapy.

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