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LETTER TO THE EDITORS

Unplanned pregnancies in kidney transplanted patients treated with everolimus: three case reports

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Dear Sirs,

We report three cases of unplanned pregnancies in two recipients of kidney transplant from deceased donor treated with everolimus (the first patient had a second pregnancy). They were in good health without particular complications related to the immunosuppressive therapy. The patients were referred to our institution at the end of the first trimester of gestation. At that time, the recipients decided to continue the pregnancy, although aware of the potential risk for developing congenital abnormalities related to the exposure of everolimus. The follow-up program included a weekly examination in collaboration with a gynecologist

Table 1. Main characteristics of the patients and outcomes of the newborns.

	Case 1	Case 2 (2nd pregnancy of patient of case 1)	Case 3
Cause of ESRD	Systemic lupus erythematosus	Systemic lupus erythematosus	Unknown
Age at transplant	28	28	26
Immunosuppressive regimen	Cyclosporine, everolimus, corticosteroids	Cyclosporine, everolimus, corticosteroids	Cyclosporine, everolimus, corticosteroids
Concomitant treatment at conception	Lansoprazole, low-dose aspirin	Calcitriol, lansoprazole	Atorvastatin, low-dose aspirin
Serum creatinine before pregnancy (mg/dl)	0.6	0.69	0.68
Creatinine clearance before pregnancy (ml/min)	105	114	117
Proteinuria before pregnancy (mg/24 h)	112	198	62
Systolic blood pressure before pregnancy	120	120	120
Diastolic blood pressure before pregnancy	80	80	80
Age at pregnancy (years)	32	35	32
Years between transplant and pregnancy	4	7	6
Concomitant treatment during pregnancy	Lansoprazole, enoxaparin, folic acid, and vitamin B12 supplements	Lansoprazole, calcitriol enoxaparin, folic acid, and vitamin B12 supplements	Enoxaparin, iron, folic acid, and vitamin B12 supplements
Serum creatinine after pregnancies (mg/dl)	0.6	0.88	0.7
Creatinine clearance after pregnancies (ml/min)	151	98	133
Proteinuria after pregnancies (mg/24 h)	255	189	192
Systolic blood pressure range during pregnancy (mm/Hg)	100–120	110–150	100–140

Table 1. continued

	Case 1	Case 2 (2nd pregnancy of patient of case 1)	Case 3
Diastolic blood pressure range during pregnancy (mm/Hg)	60–80	60–90	60–90
Apgar score	9	10	8/9
Weight at birth (gr)	3020	2980	1800
Length at birth (cm)	ND	48	46
C0 cyclosporine level (range) ng/ml	20–93	24–92	28–144
C2 cyclosporine level (range) ng/ml	81–478	161–754	187–626
Everolimus level (range) ng/ml	2.7–7.8	1.8–5.3	1.5–4.6
Type of delivery. Outcome	Term, natural. No congenital abnormalities	Term, natural. No congenital abnormalities	Cesarean section at 36th week for Intrauterine growth retard. No congenital abnormalities
Current age of the babies	3 years	9 months	1 year

who performed fetal ultrasound. They received enoxaparin throughout the gestation because the first patient had detectable lupus anticoagulant and the second had a previous deep vein thrombosis. We observed an expected reduction in the blood levels of cyclosporine and everolimus. The dosage of cyclosporine was adjusted to maintain a C2 level of about 500 ng/ml. The dosage of everolimus was not adjusted and was intentionally maintained low. Both patients had normal blood pressure without antihypertensive therapy before, during, and after pregnancy although a small increase was observed in the last trimester. The first patient had a natural deliver at term in both pregnancies. The second patient underwent a Cesarean section at the 36th week for intrauterine growth retardation. All the three babies are now in health and in the right percentile of weight. In Table 1 are shown the main characteristics of the patients and data of renal function before and after the delivery and the outcomes of the newborns.

There are few reports of pregnancies under sirolimus therapy. Sifontis [1] described seven cases of whom three had a miscarriage and four had a live birth. No malformations were observed when sirolimus was suspended or switched to azathioprine in the first trimester. The only newborn that had microtia, cleft lip, and palate was born from a recipient switched from mycophenolate to sirolimus at the 24th week. No data on renal function are reported. Chu [2] and Guardia [3] published two cases of successful gestations of living donor recipients treated with sirolimus during the entire pregnancy without alteration of renal function. Framarino [4] reported of a healthy newborn to a kidney transplanted woman with moderate graft failure (serum creatinine 3.0 mg/dl), who received sirolimus throughout the pregnancy and had a Cesarean delivery at 37 weeks for an increase in serum creatinine that regressed after delivery. Jankowska [5] described an uneventful pregnancy of a liver transplanted patient under sirolimus therapy.

Even, less cases of pregnancies under everolimus therapy were reported. One is a previous report of the first case presented in this letter [6]. In the case published by Veroux [7], an increase in serum creatinine at week 30 leads to a Cesarean delivery. Margoles [8] published an uneventful pregnancy with everolimus and azathioprine. Although our three uneventful pregnancies of patients under everolimus therapy are promising, more data are needed to determinate whether the use of mTOR-inihibitors is safe during pregnancy.

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