Tacrolimus as Basic Immunosuppression in Pregnancy After Renal Transplantation. A Single-Center Experience


ABSTRACT
Renal transplantation restores fertility within an average of 6 months, so women of childbearing age are able to consider pregnancy. Successful pregnancies have been reported in recent years under different immunosuppressive regimens, but the optimal treatment to achieve the maximum safety for both the mother and fetus remains unclear. Tacrolimus has been demonstrated to provide long-term immunosuppression and prevent rejection in most renal transplants. It seems safe, but experience is limited compared with cyclosporine. We report our experience highlighting the high rate of successful pregnancies attained in women treated with tacrolimus as the basic immunosuppressant and advised of recommendations to achieve a healthy newborn. Renal function was preserved during the pregnancy. The puerperal period and the rate of gestation-related difficulties appeared similar to that of the general population.

SUCCESSFUL pregnancy is one of the most relevant signs of rehabilitation after renal transplantation. There are relatively scarce reports of experience with tacrolimus-based therapies as the principal immunosuppressive regimen in the management of pregnant RT women. However, the increasing use of this drug in recent years has led to a greater proportion of pregnant RTs receiving tacrolimus (TAC) as basic immunosuppression. We report our experience with consecutive pregnancies from 1997 when TAC became available in Spain to 2004.

PATIENTS AND METHODS
Between 1997 and 2004, a total of 19 gestations were studied in 16 patients. Pregnancy was advised for transplant women of childbearing age according to the European Best Practice Guidelines (EBPG) criteria for renal transplantation, already summarized in a report about the complete series of our group. During pregnancy, patients were monitored monthly both in the Renal Transplantation Outpatient Department and in the Obstetrics office. The TAC blood levels were monitored monthly.

RESULTS
Mean time from transplantation to pregnancy was 3.7 (2–6.3) years, and mean age at transplantation was 30.6 (20–39) years. Renal function was normal in every patient, indicated by a mean serum creatinine of 1.07 mg/dL (94.7 μmol/L) and negative or minimal proteinuria (mean 0.15 g/d). Seven cases of mild hypertension (36.8%) were detected among RT recipients; these were controlled with just one drug. The other 12 patients were normotensive.

Immunosuppressive therapy was based on TAC and prednisone in all patients, except one who received TAC monotherapy. Prednisone was associated with the anticalcineurin drug in the remaining patients.

Outcome of Pregnancy
Successful delivery was attained in 10 gestations, with appropriate birth weight and no malformations. The failed gestations were secondary to 4 spontaneous abortions (all of them during the first trimester) and 5 therapeutic pregnancy-interruptions owing to hemolytic-uremic syndrome in 1 patient, radiation in 2, severe pre-eclampsia in 1, and high risk of cardiac malformations in another patient. Five cases of pre-eclampsia developed in our patients (26%), requiring close monitoring of blood pressure, renal function, proteinuria, uricemia, hemogram, biochemistry, and clinical status. All but one was successfully completed; in one patient, labor was induced as a consequence of renal insufficiency and increasing proteinuria. Only 3 patients (16%) developed gestational diabetes, which resolved at month 3 after delivery.

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Transplantation Proceedings, 37, 3754–3755 (2005)
No acute rejection episode was observed either during pregnancy or during the puerperal period. During pregnancy, TAC dosing needed to be increased to achieve therapeutic levels of 5 to 10 ng/mL. Mean daily dose of TAC at pregnancy diagnosis was 4.2 mg vs 7.1 mg at delivery. Neither hematological nor neurological toxicity was observed. All the fetuses were born without anomalies and with no need of breathing support.

Long-Term Outcome

At a mean follow-up of 45.6 months, 10 patients with term pregnancies all maintained their allograft with good renal function.

DISCUSSION

Successful pregnancies have been reported in renal transplanted women in recent years. Tacrolimus administration during murine pregnancy showed that high dosages (1.28 mg/kg/d by intramuscular injection) did not produce obvious detrimental effects on maternal health, but caused resorption of all fetuses, whereas in a lower-dosage group (0.16 mg/kg/d), the fetuses that survived did not appear to be different from controls. This study concluded that TAC may have adverse events on pregnancy, but that maternal and fetal toxicities were dose-dependent. Less experience exists in vivo with TAC compared with cyclosporine. There are few publications reporting a successful pregnancy with TAC. Women of childbearing age who desired to get pregnant were advised to consider pregnancy when all criteria were met. They received complete support from our team. Excluding the therapeutic abortions, we report 10 of 14 successful pregnancies (71.4%), all of them following the recommendations of the Transplant Unit.

The evolution of gestation was positive, with live births at term in most cases and no perinatal deaths. The rate of pre-eclampsia was similar to that published with other immunosuppressive treatments. In 90% of the cases, birth weight was appropriate for the gestational age.

The incidence of acute rejection episodes during pregnancy and 3 months after delivery varied between 9% and 14.5% in published series. We had no episodes of acute rejection, possibly because of the prophylactic increase in steroid doses during labor and puerperal periods, with close adjustment of TAC doses, to achieve target levels of 5 to 10 ng/mL. In addition, renal function did not suffer significant damage either on successful term delivery or with abortion. On long-term follow-up, renal function was stable, with no difference in serum creatinine, proteinuria, or blood pressure from nonpregnant transplanted women. There were just 3 cases of gestational diabetes, which solved 3 months after delivery.

Our results suggest that pregnancy under tacrolimus-based immunosuppression is safe and effective with close monitoring. It has a favorable outcome without any important effects on intrauterine growth and without a major incidence of malformations. The incidence of abortion and pre-eclampsia seemed to be similar to the general population. No relevant pharmacological side effects were produced with close monitoring of clinical and biochemical data. We emphasize the importance of coordination between the nephrology and obstetrics teams to obtain the most favorable outcome.

REFERENCES