Impact of Pregnancy on the Function of Transplanted Kidneys

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ABSTRACT

Introduction. This study reviewed the course of pregnancies in terms of impact on renal function and delivery-related data among women who received kidney transplants in our unit.

Methods. We reviewed the medical records of women transplanted between 1982 and 2002 who became pregnant. We recorded the data of medical, obstetrical, and transplant-related complications, plasma creatinine levels, and blood pressures at baseline, delivery, and 12 months after delivery.

Results. Thirty women had 37 pregnancies. Immunosuppressive protocols included cyclosporine, ketoconazole, azathioprine, and prednisone in 22 patients or azathioprine and prednisone in 15. Renal function decreased significantly: mean creatinine levels at baseline, delivery, and after 1 year were: 1.19 ± 0.38 mg/dL; 1.44 ± 0.70 mg/dL; and 1.38 ± 0.53 mg/dL, respectively ($P = .023$ and $P = .004$ vs baseline respectively). Systolic and diastolic blood pressures at delivery were higher than at baseline (134 ± 19 and 86 ± 14 mm Hg vs 126 ± 21 and 79 ± 13 mm Hg ($P = .029$ and $P = .053$, respectively). These values normalized 1 year later (128 ± 21 and 80 ± 16). Decreased use of antihypertensive drugs were the cause of poor blood pressure control (1.8 ± 1.3 vs 0.9 ± 0.7, $P < .01$). Blood pressure control improved following delivery. The most frequent complications were preeclampsia (18, 9%), intrahepatic cholestasis (13.5%), and urinary tract infections (13.5%). There were five rejection episodes. Seven miscarriages took place and one mole. Eleven pregnancies were uncomplicated.

Conclusion. Renal transplantation is the best treatment for fertile women with end-stage renal disease who want to become pregnant. However, pregnancy is risky for the mother, fetus, newborn, and allograft.

FERTILITY IS IMPROVED among women with successful kidney transplants compared with those remaining on dialysis.[1] Nevertheless, these pregnancies are at high risk of fetal and maternal complications, such as preterm delivery, low birth weight, urinary tract infection, other infections, and high blood pressure.[1] Moreover, the impact of pregnancy on allograft function is controversial. Some studies suggest that pregnancy does not negatively affect kidney function,[2–4] but another work suggests the opposite.[5] At the same time, changes in the distribution volumes of the main immunosuppressive drugs occurring during pregnancy may predispose to acute rejection episodes, jeopardizing long-term allograft survival.[6]

It is possible to decrease those risks if pregnancy is delayed until 2 years after transplantation, because renal function is adequate; stable immunosuppression may be then administered at maintenance levels.[1] The aim of our study was to review the progress of pregnancies in women who received a kidney transplant in our unit, recording the impact on kidney allograft function and also delivery-related data.

METHODS

We reviewed the database of our kidney transplant unit for patients who became pregnant between 1982 and 2002. We recorded data of medical, obstetrical, and transplant-related complications, plasma

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creatinine levels, and blood pressures at baseline, delivery, and 12 months after delivery.

We used mean values, standard deviations, and proportions with Fisher exact tests and paired Student *t* tests to assess the evolution and frequency of complications of pregnancies and of kidney transplants. All patients gave informed consent for the utilization of clinical and laboratory data from their medical records or database.

RESULTS

Between 1982 and 2002 251 (46%) of the 545 kidney transplants were in women. There were 37 pregnancies in 30 women. The source of these allografts was cadaveric donors in 14 patients (47%) and living related donors in 16 (53%). The mean period between transplantation and conception was 46.6 ± 35.5 months (range 6 to 108). Mean HLA mismatches were: locus A = 1.1, locus B = 0.9, and locus DR = 0.6. Immunosuppressive protocols included cyclosporine, ketoconazole, azathioprine, and prednisone in 22 patients (59.5%), and azathioprine and prednisone in the other 15 (40.5%). Following a diagnosis of pregnancy, ketoconazole and angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists were withdrawn. Cyclosporine doses were adjusted periodically to maintain drug blood levels in the therapeutic range.

We observed a significant decrease in renal function among the patients: mean creatinine levels at baseline, delivery, and 1 year after were: 1.19 ± 0.38 mg/dL, 1.44 ± 0.70 mg/dL, and 1.38 ± 0.53 mg/dL, respectively ($P = .023$ and $P = .004$ vs baseline, respectively).

Both systolic and diastolic blood pressure at delivery were higher than at baseline (134 ± 19 and 86 ± 14 mm Hg vs 126 ± 21 and 79 ± 13 mm Hg, $P = .029$ and $P = .053$, respectively). One year later the blood pressure was no longer statistically different from baseline (128 ± 21 and 80 ± 16). The poorer blood pressure control during pregnancy was related to the decreased use of antihypertensive drugs (1.8 ± 1.3 vs 0.9 ± 0.7, $P < .01$). However, blood pressure control improved following delivery.

Eleven pregnancies (29.7%) had no medical, obstetrical, or transplant-associated complications. The most frequent complications were: preeclampsia (18.9%), intrahepatic cholestasis (13.5%), and urinary tract infections (13.5%). There were 5 (13.5%) acute rejection episodes, three of them in the cyclosporine group.

There was one case of hidatidiform mole and seven instances of miscarriages (18.9%) including six in the cyclosporine group (27.3%) and one in the other cohort (6.7%; $P = .665$). Mean gestational age was 30.2 ± 10.3 weeks (range 8 to 39). Among the pregnancies that did not ended in abortions, mean gestational age was 35.1 ± 3.2 weeks (range 28 to 39). Deliveries were vaginal in 45% of cases and by cesarean section in the other 55%. Preterm delivery took place in 56% of patients. Newborns were boys in 56% of cases and girls in the other 44%. The mean birth weight was 2463 ± 849 g (range 600 to 3490).

DISCUSSION

Although kidney transplantation improves the reproductive prognosis for patients with renal failure, these pregnancies require multidisciplinary care by obstetricians and nephrologists, because of the frequent complications (70.3% in our series). Fortunately, most complications are those usually observed in high-risk pregnancies and well known to medical teams. One exception could be the five cases of intrahepatic cholestasis of pregnancy, but our rate of 13.5% of pregnancies is the expected rate in Chile, where this pathology is more common than in other countries.[7]

The total miscarriage rate of 18.9% is close to the 15% rate reported in the literature.[8] Rates in both groups were not significantly different, suggesting that ketoconazole does not impair the first-trimester survival of the embryo, beyond its possible interference with estrogen and progesterone synthesis by the mother. We confirmed the high rates of prematurity and low birth weight. For this reason it is recommended that all deliveries should take place in specialized centers.

Both systolic blood pressure and diastolic blood pressure decrease during normal pregnancy. Therefore it is common practice to lower antihypertensive drugs until the third trimester, when blood pressure begins to rise due to the risk of preeclampia. This behavior could explain why blood pressure control deteriorated in our patients, but it is also possible that treating nephrologists did not want to predispose women to poor uteroplacental blood flow derived from too tight blood pressure control. Anyway, after delivery the usual medications can be restarted, especially angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, to achieve proper blood pressure goals. Our policy is to discourage breast-feeding in these women.

The diagnosis of preeclampsia can be difficult in kidney graft women, mainly in patients with preexisting hypertension, proteinuria, or chronic allograft dysfunction, and also because cyclosporine induces hyperuricemia.[9] These issues can explain why we found only 18.9% of preeclampsia instead of the expected 27% to 38%.[10]

From the kidney transplant point of view, we observed that pregnancy is associated with a decreased glomerular filtration rate at delivery time, measured by serum creatinine, which did not recover until 12 months. We decided not to follow serum creatinine levels after the first year because of the many variables that could influence renal function and introduce interpretative biases. Our experience includes a similar number of pregnancies to other reports,[2–5] and although we do not have a control group of patients without pregnancy, we share the conclusions of Salmela et al[5] that pregnancy may produce deterioration in long-term renal function and decrease of graft survival.

In conclusion, we feel that kidney transplantation is the best treatment for end-stage renal disease patients, particularly fertile women wishing to get pregnant. Nevertheless, pregnancy is risky to the mother, fetus, newborn, and also the allograft. The decision of how to proceed must be based

up on a case-by-case evaluation. Also, pregnancy, delivery, and follow-up should take place in specialized centers.

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