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Pregnancy in recipients of kidney transplantation: effects on the mother and the child

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Nefrología 2008; 28 **(2)** 174-177

SUMMARY

When the field of transplantation was first developing, physicians worried about the teratogenicity of immunosuppressive medications and considered pregnancy ill-advised. The purpose of this study is to analyze pregnancy after kidney transplantation and their consequences on mother, graft and child. We rewiew ten pregnant women with kidney transplantation, average of 29 years old and 44 months post-kidney transplantation. The mean glomerular filtration rate was 64 ml/min and the immunosuppression was with prednisone and tacrolimus. We analyze outcomes of differents variables before and during pregnancy, and after labour. Pregnancy finished in nine of ten patients. Three patients needed cesarean section and only one patient had a miscarriage on the first term. Blood arterial pressure increased at the end of pregnancy and the creatinine level was stable with a few increase of proteinuria at the third term. We increased the tacrolimus dose to obtain the correct blood levels and any rejection was detected. We had only one patient with preeclampsia that we solved with a cesarean section. Labours were a mean of 37.2 weeks and the mean birth weight of infant was 2,809 g. Two newborns had prematurity without structural malformations. Pregnancy after kidney transplantation is safe with prednisone and tacrolimus when the renal function is good, proteinuria doesn't exist and blood pressure is controlled.

Key words: *Pregnancy. Transplantation. Kidney.*

RESUMEN

El embarazo se contraindicaba en los inicios del trasplante renal, pero actualmente la gestación es una parte más de los beneficios que aporta el mismo. El objetivo del estudio es analizar la viabilidad del embarazo post-trasplante renal y sus consecuencias a nivel de la paciente, el injerto renal y el neonato. Se revisaron diez pacientes trasplantadas renales embarazadas con una edad media de 29 años y un tiempo medio post-trasplante de 44 meses. El filtrado glomerular estimado medio fue de 64 ml/min y la inmunosupresión fue con corticoides y tacrolimus. Se analizó la evolución de diferentes variables durante los meses de gestación y después del parto, inherentes a la madre, al injerto renal y al recién nacido. El embarazo llegó a término en nueve de las diez pacientes, seis por vía vaginal y tres con cesárea, con solo un aborto espontáneo en el primer trimestre. La presión arterial aumentó al final del embarazo y la creatinina se mantuvo estable durante los nueve meses con un incremento de la proteinuria a partir del tercer trimestre del embarazo. La dosis de tacrolimus se tuvo que aumentar en el tercer trimestre del embarazo para conseguir los niveles deseados y no se detectó ningún rechazo agudo durante el seguimiento, apareciendo como única complicación una pre-eclampsia que se resolvió con una cesárea. El parto tuvo lugar a las 37,2 semanas de media y los recién nacidos presentaron un peso medio de 2.809 g, destacando dos recién nacidos afectos de prematuridad/bajo peso al nacer sin surgir ninguna complicación de interés en los neonatos. El embarazo post- trasplante renal es seguro con una pauta inmunosupresora basada en esteroides y tacrolimus, con buenos resultados cuando antes del embarazo la función renal es correcta, no hay proteinuria y la presión arterial está controlada.

Palabras clave: Embarazo. Trasplante. Riñón.

INTRODUCTION

In the first ages of renal transplantation pregnancy was contraindicated, however the first offspring of a renal transplanted woman was born 48 years ago[1] and since then the concepts have progressively changed, so that nowadays it is considered that pregnancy is just another positive aspect of kidney transplant; there are still several concerns about its effects on the mother and the fetus.[2] The patients with advanced chronic renal disease present hypothalamic-gonadal dysfunction leading to infertility in virtually all cases; however, 6

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Table I. Evolution of deferent variables before, during, and after the pregnancy

	Basal	Month 3	Month 6	Delivery	Month 3	1st Year
Creatinine (µmol/L)	97.9 (75-124)	83.1 (50-101)	83.7 (52-106)	97.4 (62-128)	107 (94-135)	112 (92-141)
Proteinuria (g/day)	0.12 (0.01-0.33)	0.15 (0.07-0.28)	0.25 (0.15-0.61)	0.69 (0.1-3.32)	0.28 (0.1-0.8)	0.12 (0.04-0.26)
SBP (mmHg)	119 (90-140)	119.2 (90-140)	120.3 (100-140)	131.1 (111-160)	121.7 (90-140)	119.1 (100-135)
DBP (mmHg)	73.5 (60-85)	70.9 (50-82)	70.1 (52-85)	77.9 (52-94)	76.4 (60-90)	73.1 (60-80)
TAC dose (mg/day)	6.4 (4-13)	6.6 (4-12)	9.1 (6-16)	10.1 (7,5-18)	7.64	
TAC levels (ng/mL)	8.3 (6.3-12.9)	6.2 (4.1-8.2)	5.4 (3.8-8.8)	6.4 (3.3-9.7)	8.8	

TAC: Tacrolimus.

months after the transplant this gonadal dysfunction disappears giving rise to the possibility of conception.

The most accurate data have been obtained from three specific registers on pregnancy and transplantation (the European, the American, and the British)[3-5] reporting on the peculiarities that pregnancy entails for kidney-transplanted patients. The most relevant data show that 24%-34% of them present a therapeutic or spontaneous miscarriage, the prevalence of AHT is high, preeclampsia is increased, and in more than 50% of the cases prematurity and low birth weight will occur.

MATERIAL AND METHODS

An observational prospective study was carried out analyzing 10 kidney-transplanted patients that got pregnant, with a mean age of 28.9 years (18-36). The average post-transplantation time was 44 months (12-113). The mean glomerular filtration rate estimated by the MDRD equation was 64 mL/min (49-82), and the immunosuppressive therapy that was given to all patients was prednisone 5 mg/day and tacrolimus (variable dosing to achieve plasma levels of 6-8 ng/mL).

We assessed different variables related with the renal graft, during both the pregnancy months and after the delivery (renal function, proteinuria, blood pressure, tacrolimus doses and levels), as well as other variables related with the delivery and the neonate.

The results are expressed as means, with the minimal and maximal values between brackets.

RESULTS

After revising the course during gestation and the months after, we observed that pregnancy was completed in nine patients and there was one spontaneous miscarriage during the first trimester. The delivery was through natural way in 6 cases and a cesarean section was needed in 3 patients.

The analysis of the blood pressure revealed an increase towards the end of the pregnancy, of both the systolic BP and diastolic BP (table I). Only one patient was on hypotensive therapy before the pregnancy (amlodipine), which was maintained through it, adding alpha-metildopa during the third trimester. The remaining patients were not on anti-hypertensive therapy before the pregnancy and it was necessary to prescribe alpha-metildopa in one patient during the third trimester, requiring an emergency cesarean section due to preeclampsia.

Table I shows the renal function monitoring, which remained stable during the pregnancy, and proteinuria, which slightly increased during the third trimester. This table also shows that the dose of tacrolimus had to be increased to achieve the target plasma levels. There was no case of acute rejection and there was only one case of preeclampsia that was resolved with the cesarean section.

The delivery occurred at 37.2 (34-40) weeks, and the newborns weighed 2,809 (2,040-3,760) grams, with two newborns affected of prematurity-low birth weight. However, none of these neonates had remarkable complications.

DISCUSSION

Our experience on the follow-up of post-transplantation pregnancy using prednisone and tacrolimus is satisfactory since there have not been any complications, either in the mother or the fetus. This is likely due to the fact that the patients met the recommendations set forth by both the «Report on the AST Consensus Conference on Reproductive Issues and Transplantation»[6] and the European Guidelines[7] for considering a pregnancy after renal transplantation (table II).

When analyzing the different published reviews of kidney-transplanted patients, we observed that high blood pressure is prevalent among patients on calcineurin antagonists, varying 47%-73% according to the different registers.[8-11] In our study, we observed an increase in both systolic and diastolic blood pressure. Preeclampsia occurs in 30% of pregnant transplanted patients,[11,12] being a difficult diagnosis since blood pressure tends to increase after week 20, and many patients already

Table II. Criteria for considering pregnancy in renal transplant recipients

- Stable renal function with creatinine < 1.5 mg/dl (< 133 µmol/L).
- No episodes of acute rejection within the last six months.
- Blood pressure: normal or controlled with only one antihypertensive drug.
- Proteinuria < 0.5 g/day.
- Normal ultrasound of the renal graft.
- Tecommended immunosuppression regimen:
  - Prednisone < 15 mg/day.
  - Azathioprine < 2 mg/kg/day.
  - Cyclosporin or Tacrolimus within therapeutic levels.
- MMF and mTOR inhibitors are contraindicated (they should be discontinued six weeks before conception).

have mild proteinuria before the pregnancy, in addition to increased uric acid levels. Arterial hypertension may explain, at least in part, the fact that more than half of the pregnancies end up before the due date. The management of AHT has to be aggressive[13] and metildopa, labetalol, and calcium-channel blockers may be safely used.[14] Angiotensin-renin system inhibitors are formally contraindicated after the first trimester of pregnancy and, id possible, they should be discontinued before conception. Since the effective plasma volume is decreased during the pregnancy, diuretics are not recommended either, with the exception of thiazides if the patient was taking them before.

When analyzing the renal function, we may highlight that in those patients with pre-existent renal dysfunction (creatinine > 1.5 mg% - > 133 µmol/L) the risk for graft loss is increased, during both the pregnancy and after it, so that pregnancy is not recommended in patients with values higher than these. Although a study[15] published in 1993 reported that the graft survival at 10 years was lower in patients that had got pregnant, as compared with those that had not, recent publications[16,17] show that the survival rates for the graft and the patient after 15 years of follow-up are the same in transplanted patients that got pregnant after the transplant and in those that did not. Graft dysfunction may be difficult to detect during the pregnancy given that usually creatinine levels go down during gestation, particularly during the first and second trimesters, as is observed in our sample; sometimes rejection only manifests as mild increases of plasma creatinine levels. If rejection presents, it usually responds to methylprednisolone. The safety of anti-lymphocytic globulins and rituximab is unknown.

Adequate immunosuppression levels are necessary during the pregnancy. As observed in our analysis, the plasma levels of calcineurin antagonists may vary since during gestation there are changes in the distribution volume and the extracellular volume.[7,18] However, most of the studies published have not recorded these levels. In our study, after analyzing the levels of tacrolimus, we observed that the doses must be increased in order to reach the target range, which is in agreement with those works monitoring this treatment.[19] On the other hand, in a study carried out in 21 patients without modifying the dose of tacrolimus, no episodes of acute rejection were observed.[20]

According to the published guidelines, although gestation in a kidney-transplanted patient should be considered a high-risk pregnancy, the cesarean section would only be indicated for obstetric reasons; however, although in our series this occurred in 33% of the patients, other series have reported to occur in 50% of the deliveries.

The final outcome of only 10% of miscarriages in our series differs from the data obtained when reviewing the European, American, and British registers,[3-5] in which spontaneous or therapeutic abortion occurs in 24-34% of pregnant women.

In our experience, only two patients had non-complicated urinary tract infection. The pregnancy in the kidney-transplanted patient increases the risk for infection, especially bacterial infections. About 40% of pregnant women have urinary infection, particularly in patients with chronic pyelonephritis or vesicouretheral reflux as the primary cause of renal disease (a criterion that was met by our two patients). For this reason, it is recommended to perform a sediment analysis and urine culture monthly, and if asymptomatic bacteriuria is present to treat with antibiotics for two weeks and then administering them prophylactically until delivery.[7]

When analyzing the fetal complications, we may highlight that the risk for prematurity and low birth weight is higher than 50%, and that for delayed intrauterine growth higher than 20% according to the different series,[4,21] the percentage in our modest sample being of 22%.

All immunosuppressants go through the placental barrier, so that the fetus is exposed to the toxicity of the different drugs. With prednisone, 90% of the dose administered is metabolized at the placenta before reaching the fetus; however, there have been cases reported of adrenal suppression in the fetus. With calcineurin-antagonists, plasma levels have been detected in the fetus, although at a concentration lower than in the mother.[22] The potential adverse effects may vary from major malformations to neurocognitive defects that may be only detected after birth. According to the European Guidelines, if the immunosuppressive therapy is based on calcineurin antagonists, with or without steroids or azathioprine, the patient may continue with the same treatment throughout the pregnancy. Other drugs, such as mycofenolate mofetil or mTOR inhibitors are not recommended.[7]

We did not observe any malformation in the newborns. According to the American Register, the prevalence of structural malformations is 4-5%, very similar to the figure of 3% in the series of pregnancies in the general population.[4,23] However, although a particular pattern of malformation has not been shown to be associated with prednisone, azathioprine or calcineurin antagonists, some malformations have been related with the administration of mycofenolate mofetil, so that it is recommended to discontinue this drug before conception. [24] The long-term effects from the exposure to immunosuppressants during the pregnancy are unknown. In a study carried out on 48 children followed for an average time of 5.2 years,[25] no structural or developmental abnormalities were observed, although in this series the prematurity rate was 56%. In the American Register,[4] four percent of the newborns from a cohort of 164 patients transplanted with different solid organs had some structural abnormality, although long-term follow-up of these children is not available. In another study on 175 children exposed to cyclosporin during gestation,[26] 71 attended the primary school (5-12 years) and 24% of them had delayed mental development. Although not conclusive, these data do indicate that it seems necessary that these children have a long-term neurocognitive follow-up. It is likely that the data from the registers underestimate complications such as delayed fetal development, preeclampsia, and premature births, all of them risk factors for neurocognitive impairment.

Although our experience with only 10 cases has been satisfactory, we may comment on two final issues. In the first place, many kidney-transplanted patients are not receiving the same immunosuppressive regimen as ours, either because of early withdrawal of steroids, or because of the combination with mycofenolate mofetil or switch from calcineurin antagonists to an mTOR inhibitor. Since there are no safety data with these regimens, they should be modified before the preg-

nancy, taking into account the risks that this modification may represent. On the other hand, the information should be exact and individualized to each patient, explaining in detail the potential risks, although preserving the mother's right to choose.

Although there are not definitive data in the literature, and given that immunosuppressants have been detected in the breast milk at variable concentrations, it seems wise to advise against breastfeeding, which was done in our patients.

To conclude, post-renal transplantation pregnancy is quite safe with an immunosuppressive regimen based on steroids and tacrolimus, with good outcomes when renal function is adequate before the pregnancy, there is no proteinuria, and the blood pressure is under control. However, post-renal transplantation pregnancy should still be considered as a high-risk gestation due to the complications that may occur in both the mother (infection, proteinuria, anemia, AHT, and acute rejection) and the fetus (prematurity and low birth weight),[7] so that it should be approached in a multidisciplinary way, and both the follow-up visits and immunosuppressants monitoring should be carried out more often.

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