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Lights and shadows in pregnancy and renal transplant

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The pregnancy in kidney-transplanted women represents the highest exponent of the normalization of the internal milieu derived from renal function recovery. By contrast with the female patient suffering from advanced renal failure or included in a dialysis program, in whom the viability of a pregnancy is exceptional, the kidney-transplanted woman may get pregnant and give birth without complications by virtue of the systemic changes derived from renal function reestablishment.

In their work in the present issue of NEFROLOGIA, Díaz *et al.*[1] report their experience with ten cases of transplanted pregnant women attending the Puigvert Foundation Center that gave birth to healthy offsprings with the exception of one spontaneous abortion during the first quarter of the pregnancy. The authors highlight the low incidence rate of complications, pointing out the need for just increasing the antihypertensive therapy in a patient and the occurrence of *de novo* hypertension in another case, which was complicated with preeclampsia and needing urgent cesarean section. With the exception of a mild and transient increase in proteinuria during the third quarter, the renal function remained stable after the pregnancy. As for the newborns, two had prematurity or low birth weight, but all of them had an uneventful course.

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Pregnancy in a transplanted woman often satisfies a maternal wish that may or may have not been achieved previously; however, the potential risks for the evolution of the kidney graft, as well as for the mother and the fetus, make necessary to overtly comment with the patient the possibility of a pregnancy and its potential consequences when she is included in the waiting list, and recalling them again after receiving the transplant. With the recovery of renal function, the reestablishment of the hypothalamic-hypophyseal-gonadal axis, and thus of ovulation, there exists the possibility of the patient becoming pregnant from the first months post-transplantation.[2] In this early stage, the higher cumulative doses of immunosuppressants, the higher incidence of viral infections (herpes, CMV, etc.), as well as, sometimes, the presence of arterial hypertension or sub-optimal renal function advises against the patient getting pregnant until at least one year after receiving the transplant.

Ideally, the pregnancy in a transplanted woman should take place in the presence of preserved renal function, serum creatinine below 1.5 mg/dL, absence of proteinuria, and normal blood pressure (table I). Minimal proteinuria (< 0.5 grams/day) that has not increased in the previous months, absence of anti-proteinuric therapy (ACEI or ARAII), or even the presence of mild arterial hypertension (TA < 130/80) controlled with only one anti-hypertensive drug could be acceptable. However, even under the most favorable conditions, kidney-transplanted women present an increased risk for developing high blood pressure and/or *de novo* proteinuria or worsening of pre-existent ones.[3]

Occasionally, transplanted women show, as in the series by Díaz *et al.*, this more favorable profile; however, it is common that the scenery under which the pregnancy occurs is more complex. Serum creatinine levels ≥ 1.5 mg/dL indicate an important reduction of the glomerular filtration rate in an average woman, predisposing her to the development or worsening of arterial hypertension and pregnancy-related proteinuria. Under these circumstances, the pregnant woman would be exposed to an increased risk for preeclampsia, with the subsequent risks for her and her fetus. Given all this, it has been established to advise against the pregnancy with serum creatinine levels ≥ 2 mg/dL due to the high risk for spontaneous abortion, delayed fetal development, low birth weight, prematurity, preeclampsia, and accelerated renal function deterioration.[3,4] It is likely that in addition to the absolute serum creatinine level before the pregnancy, estimating the glomerular filtration rate and taking into account the relevant information regarding the donor's characteristics (type of donor, age, death cause) and the clinical course of the patient (history of ATN, episodes of graft rejection and their severity, episodes of nephrotoxicity, etc.) will allow for a better knowledge of the graft status, since we are lacking a renal biopsy. Serum creatinine levels that slowly go up, even if < 1.5 mg/dL, or the development of arterial hypertension or *de novo* proteinuria, even if low, should put us on alert about the possible existence of progressive renal damage that should be appropriately assessed and identified before the patient gets pregnant.

By contrast with immunosuppressed patients, classically with azathioprine and steroids, who once overcome the initial post-transplantation stage maintained a stable renal function for many years after receiving the transplant, nowadays the current immunosuppression regimens with calcineurin inhibitors, with the subsequent risk for nephrotoxicity, and the older age of the donor popula-

Table I. Ideal conditions for the pregnancy in kidney-transplanted patients

- At least one year elapsed from transplantation.
- Being on maintenance immunosuppression with steroids, cyclosporin or tacrolimus and/or azathioprine.
- Having stable renal function, in the absence of acute rejection within the previous 6 months:
  - Serum creatinine < 1.5 mg/dl.
  - Absence of proteinuria or at least < 0.5 grams/day in the absence of antiproteinuric therapy (ACEIs or ARA II).
  - Normal BP (< 130/85) w/o medication or with low dose of a single anti-hypertensive drug.

tion determine higher hypertension prevalence and lower glomerular filtration rate.[5] The studies with protocoled serial biopsies in transplanted patients have shown a high prevalence of chronic renal damage from the very early stages (within the first year) post-transplantation, which is attributable to calcineurin inhibitors-induced nephrotoxicity, and to a lesser extent to immunological causes; besides, this damage seems to be progressive with no early signs in the reference laboratory parameters, such as creatinine or proteinuria.[6] Under this scenery of increasing histological damage, it would be advisable not to excessively delay the pregnancy after receiving the transplant.

The pregnancy risks in the transplanted population are mainly derived from the presence of a decreased renal function, including the detection of proteinuria and arterial hypertension at the time of the pregnancy.[3] The impact of the presence of carbohydrate intolerance or diabetes mellitus, as well as of obesity or smoking status, in the pregnant kidney-transplanted population has been less studied, although it may not be lower than that in the non-transplanted population, so that an effort should be made in order to avoid or control these factors. The immunosuppressive therapy administered may have an impact on the frequency of premature births, as has been reported with cyclosporin.[7] On the other hand, although the incidence of rejection episodes is low (< 5%), in some series it reaches 15%-17%, so that cyclosporin and tacrolimus blood levels should be monitored during both the pregnancy and the postnatal period in order to assure they are kept within the therapeutic range. It is common for patients to need dosage increments of calcineurin inhibitors since the steady state volume during the pregnancy is accompanied by a decrease in blood levels.[3]

The series published on pregnancies in transplanted populations have shown that there exists an increased risk for spontaneous abortion during the first quarter, which may affect up to 35% of the patients, although the pregnancy is successfully culminated in 90% of the pregnancies that overcome the first quarter[8] (table II). Beyond the 24th week of gestation, the most relevant complications are the following: an increased incidence or severity of arterial hypertension and proteinuria, including the risk for preeclampsia that may affect more than one third of pregnant women; an increased incidence of delayed intrauterine fetal development or of low birth weight, as well as of premature births that affect half of the newborns, with a higher proportion of cesarean sections over natural deliveries;[4] in addition, a higher anemia prevalence has been reported in transplanted patients, which has been related to inadequately low erythropoietin levels,[9] as well as of urinary infections that may affect 34% of this population.[10] This high-risk pregnancies oblige to a closer follow-up from both the obstetrician familiar with this type of patients and the nephrologist; the follow-up visits to both specialists should occur at least on a monthly basis, in addition to patient's monitoring of her blood pressure at home, with the possibility of more frequent visits in the case of occurrence of arterial hypertension or worsening of pre-existent high blood pressure. Those cases with high risk for preeclampsia should be admitted to the hospital for close monitoring and fetal monitoring. The delivery route should be decided according to obstetric criteria although recurring to cesarean section occurs in 50% of the patients in most series.[4] After the delivery, proteinuria uses to go back to levels similar to those before the pregnancy, although in those patients with decreased renal function (with serum creatinine levels > 1.5 mg/dL) accelerated renal function deterioration and graft failure may be observed.[11]

About the neonates of transplanted mothers, deaths during the perinatal period and an increased risk for infectious complications, especially in premature babies or those with low birth weight, have been reported.[4] Except for this, the newborns do not generally present special problems and it has been reported that the incidence of malformations is not significantly increased as compared to the general population with immunosuppressive regimens incorporating steroids, cyclosporin, tacrolimus, or azathioprine. This is not the case for IMPDH inhibitors, of which mofetil mycofenolate is the most commonly used one, since they have shown to be teratogenic in animal studies and from the clinical experience.[12] Similarly, the proliferation-signaling inhibitors, such as sirolimus and everolimus, have also shown to be teratogenic in animals, although with limited clinical experience.[13] Both groups of agents are contraindicated in the patient wishing to get preg-

Table II. Main pregnancy-derived complications kidney-transplanted patients

- Arterial hypertension or *de novo* proteinuria or worsening of pre-existent ones.
- Preeclampsia.
- Spontaneous abortions.
- Premature births.
- Intrauterine delayed development and low birth weight.
- Neonatal death.
- Anemia.
- Urinary infections.
- Acute rejection.
- Glomerular filtration deterioration.
- Increased need for cesarean section.

nant and they should be withdrawn at least six to eight weeks before the pregnancy.

The intermediate- and long-term complications from having been submitted to immunosuppressive therapy *in uterus* are unknown in babies born from kidney-transplanted mothers. Decreases in the T and B cell populations have been described within the first months of life in babies submitted to *in uterus* immunosuppressive therapy, which normalize within the first year of life, although the implications that this situation may have on the immune system in the long run are unknown.[14] The possible repercussions on the neurocognitive level and other systems from having received immunosuppressants is not known either, as well as differentiating them from the implications of the high prevalence of prematurity in the population of babies born from kidney-transplanted mothers.

This scenery allows concluding that childbearing-aged mothers receiving a kidney transplant must be informed about the possibility of getting pregnant, and the use of contraception methods, especially barrier methods, in order to avoid unwanted pregnancies. In those wishing it, the pregnancy should be planned in order to adopt the most convenient measures and avoid potentially teratogenic immunosuppressants. Besides, every patient manifesting her wish of getting pregnant must be individually informed about both the benefits derived from maternity and the risks and potential complications derived from the pregnancy, as well as the care her offspring may demand, through a frank and sincere conversation with her nephrologist, and her couple; all this considering the mother's clinical setting that may limit her quality of life and her vital outcome.

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