

# Full term pregnancy after simultaneous kidney and pancreas transplantation

P. Gutiérrez<sup>1</sup>, I. Martín-Mederos<sup>2</sup>, L. Pérez-Tamajón<sup>3</sup>, M. Coloma<sup>2</sup>, A. Alarcó<sup>4</sup>, A. Bravo<sup>4</sup> and J. M. González-Posada<sup>3</sup>

Urology Department<sup>1</sup>, Obstetric and Gynecology Department<sup>2</sup>, Nephrology Department<sup>3</sup> and General Surgery Department<sup>4</sup>. University Hospital of Canary Islands. Tenerife.

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## SUMMARY

The effects of pregnancy on kidney transplant recipients have been widely described, although its impact on the mother, the fetus and the graft is still debated. Experience in simultaneous kidney-pancreas transplantation is limited, with few reported cases, which increases uncertainty about guidelines to follow in this situation. We describe a case of successful pregnancy in a 35 year-old patient who underwent simultaneous pancreas-kidney transplantation 34 months before delivery. After modifications in immunosuppressive therapy (with tacrolimus and mycophenolate, the latter being switched to azathioprine), pregnancy evolved favourably. Delivery was by caesarean section due to fetal distress at 38 weeks of gestational age. Five months after delivery the child shows normal development while both pancreas and kidney grafts show normal function.

Key words: Diabetes mellitus. Chronic renal failure. Simultaneous kidney-pancreas transplantation. Pregnancy.

## RESUMEN

Los efectos del embarazo en receptoras de un trasplante renal han sido ampliamente descritos aunque su impacto sobre el injerto, el receptor o en el feto es aún motivo de debate. La experiencia en el trasplante simultáneo de riñón y páncreas es escasa debido al limitado número de casos publicados lo que incrementa la incertidumbre sobre la pauta a seguir en esta situación. Se describe un caso de embarazo a término en una receptora de trasplante simultáneo de riñón y páncreas de 35 años de edad a los 34 meses del implante. Tras modificaciones en el tratamiento inmunosupresor, el embarazo evoluciona favorablemente dando a luz la paciente, mediante cesárea de urgencia por sufrimiento fetal, a las semanas 38 de gestación. A los 5 meses del parto ambos injertos funcionan normalmente siendo el desarrollo del niño totalmente normal.

Palabras clave: Diabetes mellitus. Insuficiencia renal crónica. Trasplante simultáneo de riñón y páncreas. Embarazo.

## INTRODUCTION

The possibility of a full term pregnancy is one of the benefits that women can obtain after solid organ transplantation. Gonadal dysfunction is a consequence of renal failure or of other organ insufficiency and it can be recovered a few months after the graft begins to properly work.<sup>1-3</sup> The current information about pregnancy and solid organ transplantation was obtained from voluntary registers, case reports and hospital retrospective surveys. The voluntary registers were the ones that allowed the best information on this subject.<sup>1-3</sup> The accumulated experience on renal transplantation<sup>1-6</sup> is in contrast with the few reported or registered cases of simultaneous kidney and pancreatic transplantation (SKPT).<sup>1-3,6,7</sup> There are common risks for both kinds of transplants in the fetus (miscarriage, preterm labor or malformations), as well as in the mother (high blood pressure, preeclampsia and more frequent infections) and the graft (acute rejection and renal function worsening).<sup>1-3</sup> The effect of the pregnancy on graft function in case of SKPT and the problems associated to the presence of two organs within the pelvis are not clear. In the present article we present a full term pregnancy in a patient, who has undergone a SKPT, and who maintained an adequate function of

**Correspondence:** José Manuel González-Posada  
Servicio de Nefrología  
Hospital Universitario de Canarias  
Ofra, s/n  
38320 La Laguna. Santa Cruz de Tenerife. España  
[jmgposada@hotmail.com](mailto:jmgposada@hotmail.com)

**Table I. Clinical findings and blood parameters before the pregnancy, during the pregnancy at first, second and third trimesters, and three months after the delivery**

	3 months before pregnancy	1 <sup>st</sup> trimester	2 <sup>nd</sup> trimester	3 <sup>rd</sup> trimester	3 months after delivery
Antihypertensive drugs	No	No	No	No	No
Systolic blood pressure	140	130	120	130	124
Diastolic blood pressure	80	78	69	80	70
Tacrolimus doses (mg/day)	6	6	6	5.5	5
Tacrolimus levels (ng/mL)	5.8	6.4	8.2	9	6.8
MMF doses (mg/day)	1,000	0	0	0	1,000
Azathioprine doses (mg/day)	–	75	75	75	0
Plasma creatinine (mg/dL)	0.9	0.8	0.8	0.9	0.8
Uric acid (mg/dl)	6	4.8	5.6	5.5	4.9
Proteinuria 24 h (mg)	176	30	–	56	
Glycemia (mg/dL)	106	95	87	67	89
Glycosilated hemoglobin (%)	4.3	4.8	4.8	4.9	4.9

both grafts after the delivery, and we update the relevant issues on this topic.

### CASE REPORT

We present a 35 years old female in her first pregnancy. She had a history of type 1 diabetes mellitus, renal failure, and had undergone a SKPT in 2003. Pancreatic graft was placed at the intraperitoneal cavity in the right iliac fossa, and the renal graft was placed in the extraperitoneal left iliac fossa. She received immunosuppression with Thymoglobulin, tacrolimus, mycophenolate mofetil (MMF) and steroids. The steroids were withdrawn after 5 months. Twenty-six months after the intervention the patient expressed her wish of getting pregnant. At that time, she was on tacrolimus, MMF and statins, her blood pressure was normal without pharmacological treatment, she had no pathological proteinuria and both grafts had normal function. The patient was informed about the risks of the pregnancy. Treatment with statins and MMF was withdrawn and azathioprine was added. The patient got pregnant and her pregnancy was followed up at the high-risk pregnancy outpatient clinic of the Obstetrics Department and the Nephrology Department. The pregnancy went on without complications except for an episode of asymptomatic bacteriuria. In the 28th week, the patient was admitted to the hospital and the labor work began physiologically. Two hours later, sustained fetal bradycardia developed, which did not revert. The medical team on shift indicated an urgent cesarean section because of suspected loss of fetal well-being. A male of 2,980 grams was delivered, who was evaluated as normal by the Neonatology team on call. The postsurgical period was favorable for both the mother and the baby, and given the excellent evolution, they

were discharged 4 days later. On table I several interesting parameters of the patient before pregnancy, at each trimester of the pregnancy, and 5 months after the delivery are shown.

### DISCUSSION

More than 75% of the hundreds of pregnancy cases in transplanted patients, which are published or reported in different registers, correspond to renal transplants, followed by liver and heart transplant, SKPT being less than 5%.<sup>1-3</sup> That explains that the American and European guidelines<sup>8-10</sup> refer mainly to renal transplant. Although the pregnancy should be treated as high-risk, if the criteria shown in table II are fulfilled it can be considered low-risk.<sup>1,9,10</sup>

A higher risk of miscarriage, preterm labor (< 37 weeks) and low weight (< 2,500 g) has been reported in different transplant types. The frequency of preterm labor and low weight was higher in the case of SKPT and in renal transplan-

**Table II. Criteria to be considered in pregnancy and renal transplant**

- To wait at least one year after the transplantation.
- No graft rejection during the previous year.
- Stable renal function (creatinine < 1.5 mg/dL) (appropriate GFE: to be defined).
- Minimal or absent proteinuria (limit to be defined).
- Normal blood pressure or minimal need for antihypertensive drugs.
- Immunosupresion on stable doses.
- It should always be considered as a high-risk pregnancy.
- Cesarean section indicated for obstetric reasons.

GFR = Glomerular filtration rate. Modified from 9 and 10.

**Table III. Outcomes and complications of the pregnancy in the different types of transplants**

	Kidney transplant	Liver transplant	Simultaneous kidney and pancreas transplant
Spontaneous miscarriage	12-24%	19%	14%
Therapeutic abortion	1-8%	6%	5%
Pre-term (< 37 weeks)	53%	36%	78%
Low weight (< 2,500 g)	46-50%	34%	63%
Cesarean section	46-55%	46%	55%
High blood pressure	58-72%	35%	75%
Diabetes	3-12%	5%	2%
Infection	22-34%	27%	55%
Preeclampsia	29-31%	23%	34%
Acute rejection	2-4%	8%	6%
Graft loss in w years	4-13%	7%	16%

From Armenti et al.<sup>2</sup>.

tation than in liver transplant.<sup>1,2</sup> On the other hand, the frequency of high blood pressure, preeclampsia and infections is higher among patients with SKPT, while the incidence of acute rejection is similar to other transplants<sup>2</sup> (table III). In the reported case, the evolution was without complications except for the above-mentioned bacteriuria. The pregnancy went on till full term and the fetus weight was normal. That can be due to the normal renal function and the lack of hypertension and pathological proteinuria before and during the pregnancy. In this sense, a recent study shows that abnormal renal function (plasma creatinine levels > 1.69 mg/dL) and the use of antihypertensive drugs before the pregnancy are independent risk factors for preterm delivery. The reason in most cases is the performance of a cesarean section indicated because of high blood pressure, preeclampsia and renal function worsening.<sup>3</sup>

The balance between the risk for acute rejection and the teratogenic effect of the drugs is another important issue to be taken into account. It has been suggested that the pregnancy produces a state of immunosuppression. But the current evidence points out that the uterus is an «immune sanctuary», while the mother maintains a competent immunological system.<sup>1,9,10</sup> So inadequate immunosuppression can lead to acute graft rejection.<sup>1</sup> Although a great deal of immunosuppressive drugs is currently available, the adequate regime and doses are yet to be defined.<sup>1,2,11</sup> The FDA classifies the drugs into five categories according to the teratogenic risk (in animal and/or human studies) that can be summarized as follows: A = remote possibility; B = no evident risk in humans; C = a risk in humans can not be ruled out (evaluate risk/benefit); D = evident risk in humans (acceptable if the benefit is high); X = absolutely contraindicated.<sup>1</sup> Most immunosuppressive drugs are classically classified into the group C, with the exception of azathioprine, which belongs to group D.<sup>1,2</sup> However, the

FDA has recently changed the classification of MMF from category C to D (October 2007). In the reported case, the patient was not on steroids and it was decided to maintain tacrolimus levels within the therapeutic range and to substitute MMF by azathioprine. In that moment the modification was made following the European guidelines, which contraindicated MMF and recommended azathioprine,<sup>10</sup> probably because the evidence with this drug was larger. On the other hand, a recent study shows that there is a higher incidence of structural anomalies in newborns of women with transplant, who take MMF in comparison to other therapies.<sup>12</sup> Due to this fact and to the change of category made by the FDA, it is better to retain us from the use of MMF in patients with transplant, like other authors have also suggested.<sup>1,9</sup>

In conclusion, although the experience in pregnancy and simultaneous kidney and pancreas transplant is limited, we believe that if the criteria known for the renal transplantation are fulfilled, and if a immunosuppression similar to that on previous months can be maintained, avoiding the drugs, with which there is less experience, then the risks for the mother, the organs and the child, though present, can be acceptable.

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