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Challenges of pregnancy in pancreas-kidney transplant recipients: Experience from our center

Desafíos del embarazo en receptoras de trasplante páncreas y riñón. Experiencia en nuestro centro

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ABSTRACT

Background and objective: Chronic kidney disease affects up to 6% of women of childbearing age, leading to fertility issues and low pregnancy rates. In patients with diabetes mellitus and chronic kidney disease, simultaneous pancreas-kidney transplantation restores renal function and endogenous insulin production, thereby increasing the likelihood of a successful pregnancy. However, pregnancy after transplantation remains high-risk. Several factors may influence maternal and fetal outcomes, including preconception counseling, appropriate maternal medical management, and the careful selection of immunosuppressive therapy to avoid fetal toxicity. Although obstetric, perinatal, and nephrology care have improved since the first reported pregnancy in a simultaneous pancreas-kidney transplantation recipient in 1986, further research is still needed to fully understand its impact on maternal, fetal, and graft outcomes, particularly in the context of combined organ transplantation. The objective of this study is to describe the clinical course of pregnant simultaneous pancreas-kidney transplantation recipients and to evaluate both the impact of transplantation on pregnancy and the prognostic factors that may influence outcomes.

Materials and methods: We conducted a descriptive analysis of a case series involving six pregnancies in simultaneous pancreas-kidney transplantation recipients managed at our center. Renal and pancreatic graft function, as well as maternal and fetal outcomes during gestation, were summarized quantitatively and graphically. Detailed, anonymized clinical data were collected for each patient throughout the follow-up period.

Results: All pregnancies occurred more than one year after transplantation, allowing for adjustment of immunosuppressive regimens to minimize teratogenic risk. Renal and pancreatic graft function remained stable throughout the follow-up. Three patients experienced uncomplicated pregnancies. The remaining three required hospitalization due to complications: one case of hyperemesis gravidarum, one of preeclampsia, and one of threatened preterm labor secondary to polyhydramnios. Except for one, all deliveries were performed via cesarean section for obstetric indications, resulting in live, healthy neonates. Four births were preterm, with low-birth-weight infants.

Conclusions: In our experience, pregnancies in simultaneous pancreas-kidney transplantation recipients were associated with favorable maternal and fetal outcomes. Careful planning and close multidisciplinary monitoring by nephrology, endocrinology, and obstetrics are essential to optimize results during pregnancy.

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Palabras clave:
Trasplante páncreas-riñón
Embarazo
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Embarazo de alto riesgo
Manejo multidisciplinar

RESUMEN

Antecedentes y objetivo: La enfermedad renal crónica afecta hasta al 6% de las mujeres en edad fértil ocasionando problemas de fertilidad y bajas tasas de embarazo. En pacientes con diabetes mellitus y enfermedad renal crónica, el trasplante páncreas-riñón restaura la función renal y la producción de insulina endógena, aumentando así las posibilidades de un embarazo exitoso. Sin embargo, el embarazo en pacientes trasplantadas sigue siendo de alto riesgo. Diversos factores pueden influir sobre el resultado, destacando el asesoramiento previo a la concepción, el manejo médico materno y el uso correcto de la medicación para prevenir la toxicidad fetal. Aunque la atención obstétrica, perinatal y nefrológica ha mejorado desde el primer embarazo registrado en una receptora de trasplante páncreas-riñón en 1986, siguen existiendo aspectos a valorar en relación con cómo afecta a la madre, al feto o al propio injerto renal, especialmente en el caso de trasplantes combinados. En este contexto, el objetivo de este estudio radica en conocer la evolución clínica de estas pacientes, permitiendo evaluar tanto el impacto del trasplante en el embarazo como los factores que podrían influir en su pronóstico.

Materiales y métodos: Estudio descriptivo de una serie de seis casos de pacientes embarazadas tras haber recibido previamente un trasplante simultáneo páncreas-riñón en nuestro centro. Se han resumido, de forma cuantitativa y gráfica, las variables relacionadas con el injerto renal y pancreático, así como la evolución de la madre y el feto durante el período gestacional, presentando la información de cada uno de los sujetos de forma detallada y anónima durante el período de seguimiento.

Resultados: En todos los casos el embarazo tuvo lugar transcurrido más de un año después del trasplante, y su planificación permitió modificar la pauta inmunosupresora de las pacientes con la intención de evitar teratogenicidad. A lo largo del período de seguimiento, tanto la función del injerto pancreático como renal se mantuvo estable. Durante el tiempo de gestación, en tres de nuestras pacientes no ocurrieron incidencias relevantes. Sin embargo, las otras tres presentaron complicaciones que requirieron ingreso hospitalario, una de ellas por hiperémesis gravídica, otra preeclampsia y una tercera por amenaza de parto prematuro debido a polihidramnios. Salvo en un caso, todos los partos fueron por cesárea por indicación obstétrica, con un recién nacido vivo sano. Cuatro de ellos fueron partos pretérmino con bajo peso al nacimiento.

Conclusiones: En nuestra experiencia, los embarazos en pacientes con trasplante páncreas-riñón han presentado una evolución favorable. Es fundamental que el embarazo sea planificado, llevando a cabo un estrecho seguimiento por parte de nefrología, endocrinología y obstetricia durante la gestación.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease with a high prevalence and is among the main causes of chronic kidney disease (CKD) and terminal renal disease. Although type 1 DM is less common than type 2 DM, it is associated with high morbidity and mortality rates because of its microvascular and macrovascular complications, among which CKD is notable. In fact, diabetic kidney disease is the main cause of the initiation of renal replacement therapy in patients with advanced CKD in many Western countries.[1,2]

In this context, the simultaneous transplantation of the pancreas and kidney (PRT) has become the most frequent modality, representing between 75 and 80% of pancreatic transplants.[3,4] Since the first simultaneous PRT was conducted in December 1966 by Kelly et al.[5] in a diabetic patient on dialysis, which achieved a recovery of the function of both organs, this technique has evolved and has experienced a global increase in frequency in recent decades.[4]

The relationships among CKD, DM and fertility increase the complexity of the challenge of pregnancy in this context. CKD affects up to 6% of women of childbearing age,[6] causing menstrual disorders, decreased libido, sexual dysfunction and infertility, which progressively worsen with the deterioration of renal function.[7,8] Up to 90% of patients with end-stage CKD have menstrual disorders, and approximately 50% have amenorrhea.[9] Consequently, conception rates among women on dialysis are very low, ranging between 0.9 and 7%.[10] These difficulties are due to multiple factors, such as endocrine disorders (dysfunction of the hypothalamic–pituitary–gonadal axis and hyperprolactinemia), cardiovascular conditions (calciphylaxis, vascular dysfunction, and heart failure), neuropsychiatric conditions (autonomic neuropathy, depression, and anxiety), pharmacological treatment (antihypertensives, antidepressants, and immunosuppressive drugs) and other associated comorbidities (systemic lupus erythematosus [SLE]), DM and vasculitis, among others).[11]

After renal transplantation, rapid improvements in various hormonal and functional alterations related to CKD have been observed. An example is the restoration of the hypothalamic–pituitary–gonadal axis, which contributes to a reduction in sexual dysfunction, which decreases from affecting 80% of patients with CKD to only 10% after transplantation. The recovery of libido, sexual function and fertility can be rapid, which underscores the importance of adequate counseling on contraception for proper pregnancy planning.[10,12,13]

PRT restores not only renal function but also endogenous insulin production in patients with type 1 DM and CKD, thus increasing the chances of restoring fertility and achieving a successful pregnancy.[14,15] In this context, the first documented pregnancy in a recipient of simultaneous PRT dates to 1986.[16]

Several factors influence these results, and receiving guidance prior to conception is essential. Pregnancy is recommended preferably in the first or second year after transplantation[17,18] in patients with a functioning graft, without evidence of rejection, with controlled blood pressure and with stable doses of immunosuppressants that allow possible adjustments in immunosuppression to reduce the risk of fetal toxicity and minimize teratogenic effects and risks associated with pregnancy.[18]

The challenge lies in understanding and managing the complexities inherent to this situation, and a multidisciplinary approach involving the nephrology, endocrinology and obstetrics units is essential. Despite these advances, questions remain about how pregnancy can affect the mother, the fetus and the renal graft itself, especially in patients who received PRT, where the clinical experience remains limited.

Materials and methods

This retrospective and descriptive study was performed on a series of 6 patients whose pregnancies were carried to term between January 2016 and December 2023 after having previously received a simultaneous PRT.

The patients included in the study were women whose follow-up after transplantation was performed at the La Fe University and Polytechnic Hospital. After the desire and intention to be mothers were made known by the women and each case was assessed individually by the nephrologist based on the established guidelines, pregnancy could be planned and monitored at our center.

The parameters related to the function of the renal graft were measured and summarized graphically from the time of gestation until 1 year after delivery. The values of creatinine, proteinuria and glycosylated hemoglobin (HbA1c) levels were obtained at different frequencies, according to the nature of the parameters, but were measured consistently at the beginning of gestation ("Baseline"), 1 year after gestation ("12 M(B)") and 1 year after delivery ("12 M(P)").

Immunosuppressive regimen

In accordance with the protocol used at our center and given that patients had a low immunological risk, the immunosuppressive regimen consisted of induction treatment with basiliximab followed by triple therapy with a calcineurin inhibitor (tacrolimus), mTOR inhibitors (sirolimus or everolimus) or mycophenolate (mofetil or sodium) and a corticosteroid (prednisone).

Protocols for the pregestational assessment and follow-up

Upon communication of the desire to achieve pregnancy by the patients, we initially proceeded to evaluate the stability of renal function, proteinuria and immunosuppressive therapy, adjusting the medication and suspending potentially teratogenic drugs. Treatment with mTOR inhibitors or mycophenolate mofetil was replaced by azathioprine as part of the adjustment of the immunosuppressive regimen.

After therapeutic modifications, a follow-up period was established to confirm the stability of renal function and proteinuria, as well as to ensure adequate pharmacological levels. In addition, a control renal ultrasound was performed. After the period stipulated by the clinical guidelines and upon conformation of clinical and analytical stability, the patient was informed that she could attempt pregnancy safely.

Once pregnancy was confirmed, the patient was referred for an obstetric consultation, and clinical follow-up was intensified, generally with monthly visits. Depending on the clinical course or the appearance of complications, increasing the frequency of visits may be necessary. In each control, a systematic evaluation was performed that included assessments of renal function, blood pressure, body weight, urinalysis, urine culture and immunosuppressant levels, whose target values were approximately 6–7 ng/ml, adjusted according to the immunological risk profile of each patient.

Data collection and processing

Information related to the demographic, clinical and laboratory data of each patient, which was retrospectively extracted from the electronic medical records of our center, was presented in detail and anonymously during the follow-up period.

In all cases, the pregnancy of the patients occurred after receiving advice from their attending physician, indicating that the patient had a "planned" pregnancy. Renal graft function was monitored by assessing serum creatinine and proteinuria levels, while follow-up of the pancreatic graft was performed by measuring blood glucose levels and HbA1c levels before and after pregnancy and performing an oral glucose overload test.

Pancreatic graft loss was defined as the sustained need for exogenous insulin, and renal graft loss was defined as the need to start dialysis.

Intrauterine growth retardation (IUGR) was defined as a fetal weight below the 10th percentile. Preterm birth was considered to have occurred before 37 weeks of gestational age. The birth weight was considered normal if it was greater than 2.500 g, low if it was between 1.500 and 2.500 g, and very low if it was less than 1.500 G.

Both the parameters related to the renal and pancreatic grafts as well as the changes observed in the mother and the fetus during the gestational period and at the time of delivery were summarized in quantitative, qualitative and graphical forms to determine the clinical evolution of the included subjects.

The data were analyzed and the graphical representations were generated using the statistical software R (version 4.4.2).

Results

Demographic characteristics

Since 2002, a total of 152 PRTs have been performed in our center, of which 87 were performed in men and 65 in women. Between May 2015 and April 2023, 6 women became pregnant after transplantation, all of whom had a previous negative laboratory screen. The mean age of the patients included in the study at the time of pregnancy was 38.8 years, with a minimum age of 35 years and a maximum age of 44 years, while the average time elapsed from transplantation to pregnancy was 65 months.

The cause of CKD was diabetic kidney disease resulting from type I DM, which was concomitant with SLE in 1 of the patients (16.7%). Nephropathy was accompanied by a series of complications during the evolution of the disease, with retinopathy predominating in 4 patients (66.7%) and polyneuropathy in 3 (50%), and gastropathy, ulcers, infracondylar amputation and diabetic foot each occurred in 1 patient.

Regarding toxic habits, 4 patients had been smokers prior to transplantation. In no case was the smoking habit resumed later. Although 50% of the participants had arterial hypertension (AHT) prior to transplantation, a notable improvement in its control was observed after transplantation, with the need to maintain the use of antihypertensive drugs until the time of pregnancy in only 1 patient. Four patients had 1 or more episodes of urinary tract infection before pregnancy. The corresponding information is detailed in Table 1.

Characteristics of the donor and transplant

The mean age of the donors was 20.3 years. With respect to sex, 50% were male, and 50% were female. A delay in the function of the renal graft was not observed in any of the patients. With respect to pancreatic function, although all patients required insulin therapy after hospital discharge, withdrawal of treatment was achieved in all patients during the first year after transplantation.

Obstetric history and conception

Three of the patients were primiparous, while the other 3 had had a previous pregnancy that ended in abortion. Two of them experienced an abortion after the kidney transplant, while in the other patient, the abortion occurred before the transplant.

In all cases, the pregnancy was planned, with the majority being by spontaneous fertilization (n = 4) and the remaining 2 by in vitro fertilization (IVF). This planned pregnancy allowed the immunosuppressive regimen of the patients to be adjusted according to the established protocol to avoid teratogenicity.

Table 1
Demographic characteristics of the pregnant women who underwent transplantation.

Patient (ID)	1	2	3	4	5	6
Smoking habit	Previous	Previous	Previous	Previous	No	No
AHT						
Before transplantation	No	Yes	No	No	Yes	Yes
After transplantation	No	Sí	No	No	No	No
DM	Type I	Type I	Type I	Type I	Type I	Type I
RRT modality prior to PD	PD	PRE	HD	HD	PD	
Time on dialysis until transplantation (years)	2.3	1.6	NA	2.1	4.7	2.7
Age at transplantation (years)	34	37	30	37	31	31
Age at pregnancy (years)	37	44	40	40	37	35
Time from transplantation to pregnancy (months)	40	87	113	38	70	43

DM, diabetes mellitus; PD, peritoneal dialysis; HD, hemodialysis; AHT, arterial hypertension; PRE, predialysis; RRT, renal replacement therapy.

Evolution of pregnancy and renal and pancreatic grafts

Six patients who had stable renal (creatinine and proteinuria levels) and pancreatic (HbA1c, C-peptide, amylase and lipase levels) parameters reached the gestational period with functioning grafts. A prior biopsy of the renal graft was not performed in any of the patients. An oral glucose tolerance test was not conducted because of poor clinical tolerance.

Renal graft function was maintained at adequate and stable levels throughout the gestational period, as evidenced by the changes in creatinine levels (Fig. 1) and proteinuria (Fig. 2). With respect to pancreatic function, the HbA1c level before and after pregnancy remained stable (Fig. 3), as did the C-peptide, amylase and lipase levels (Fig. 4), with all patients presenting a test of normal oral glucose overload.

The functions of both the pancreatic and renal grafts remained at adequate levels from the beginning of pregnancy until 1 year after delivery. Three of the patients (50%) did not experience relevant incidents; however, the remaining patients (50%) presented complications that required hospital admission, 1 for hyperemesis gravidarum, another for preeclampsia and 1 for the threat of premature labor due to polyhydramnios.

During pregnancy, 1 of the patients presented with an episode of asymptomatic bacteriuria with isolation of *Enterococcus faecalis*, for which she received targeted treatment with ampicillin, with subsequent negative urine cultures.

Prior to pregnancy, the usual medication of the patient receiving antihypertensive treatment was replaced with methyldopa. During pregnancy, this patient and 4 others maintained adequate control of blood pressure, which remained stable until delivery. However, a sixth patient with no history of hypertension developed preeclampsia at week 28 of gestation, which necessitated hospital admission. The patient had elevated blood pressure and required perfusion with labetalol. The patient presented with a deterioration of renal function, without the appearance of complications such as HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome or placental abruption. Cesarean section was performed after neuroprotection and lung maturation were complete.

Continuous pharmacological monitoring was performed to adjust the dose of immunosuppressants to maintain pharmacological levels within the target therapeutic range, compensating for the variations that occur throughout the different stages of gestation, as illustrated in Fig. 5.

Delivery and subsequent development

For all but 1 patient, delivery was by cesarean section by obstetric indication, with live and healthy newborns. Among these cesarean sections, 4 were performed for the following reasons: premature rupture of membranes, fetal bradycardia, preeclampsia and failed induction. Among the 6 deliveries, 4 were preterm.

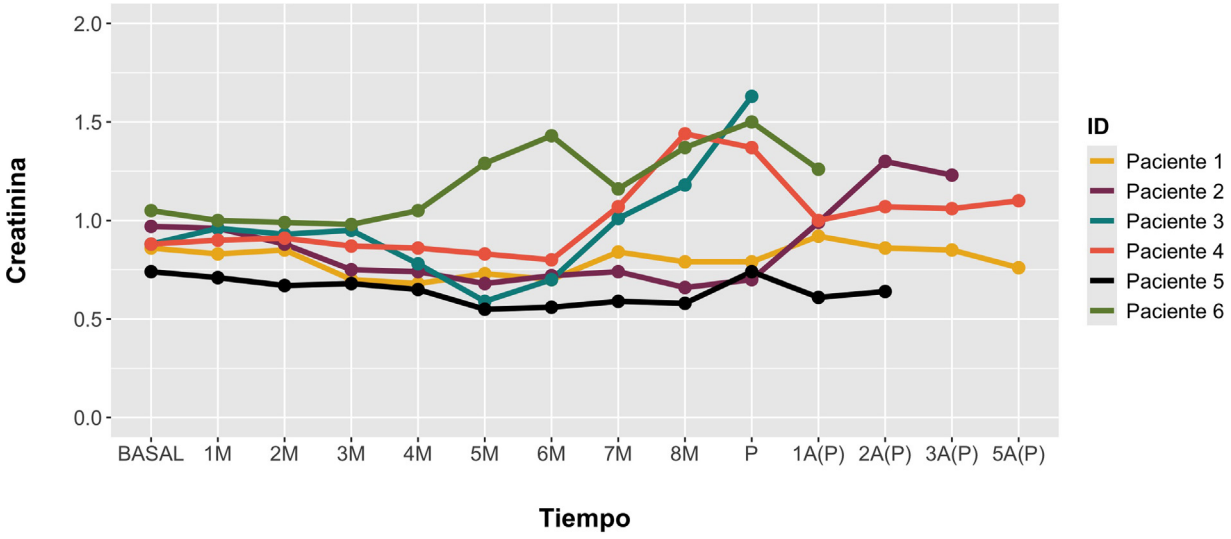


Figure 1. Changes in creatinine levels during pregnancy. Creatinine (mg/dl).

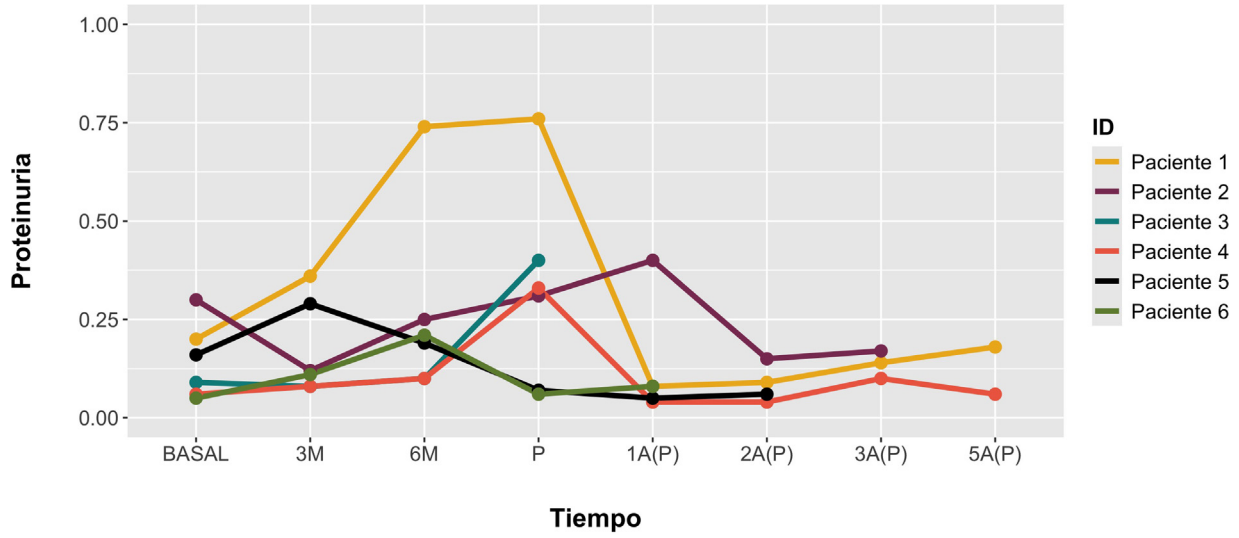


Figure 2. Changes in proteinuria levels during pregnancy. Proteinuria (grams in 24 h).

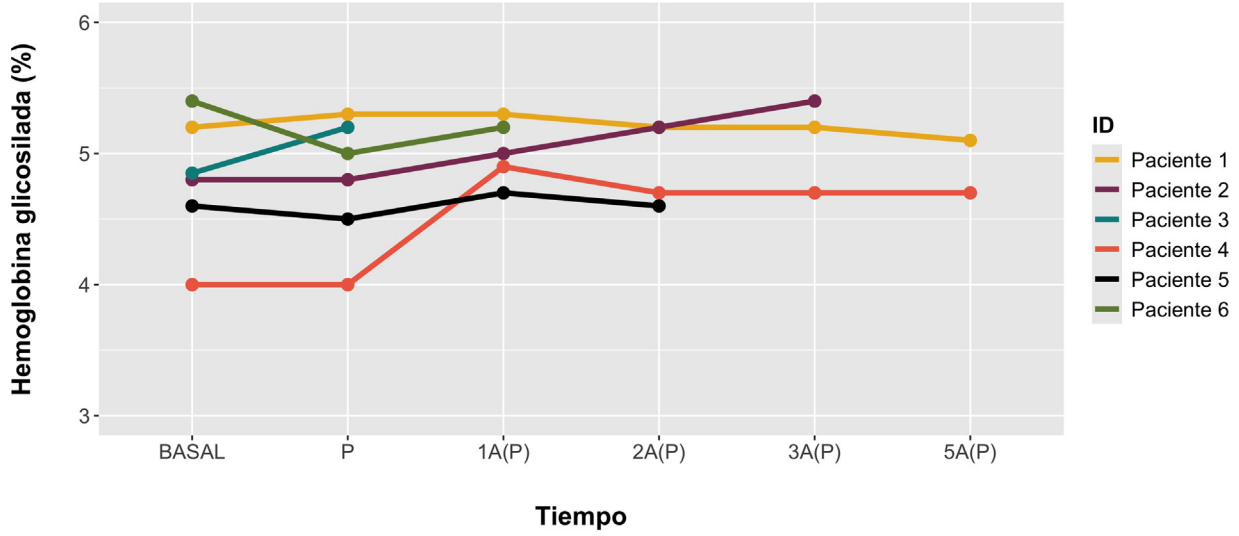


Figure 3. Changes in glycosylated hemoglobin levels during pregnancy.

One newborn was born with a normal weight, 4 with a low birth weight and 1 with a very low birth weight, but in all cases, the birth weight was appropriate for the gestational age. All newborns had a favorable outcome, with scores on the APGAR test between 6 and 10 at minute 1 and between 9 and 10 at minute 5. Four of the newborns (66.6%) were exclusively breastfed. The corresponding details are listed in Table 2.

Discussion

The present study describes the experience of a series of 6 patients who underwent PRT in relation to posttransplant conception. All of these patients had a planned pregnancy; 4 of pregnancies resulted from spontaneous fertilization, and the remaining 2 resulted from in vitro *fertilization*. In all cases, because the patients expressed a desire for pregnancy, the treatment was modified to avoid teratogenicity. All patients previously had stable creatinine, proteinuria and HbA1c levels and maintained adequate renal and pancreatic graft function during the gestational period. Regarding delivery, all deliveries except 2 were preterm. Among the newborns, 1 was born with a normal weight, 4 with a low birth weight, and 1 with a very low birth weight.

The results suggest a good pregnancy course in patients with PRT, with adequate graft function and adequate neonatal outcomes.

Pregnancy planning

Our study highlights the importance of careful pregnancy planning in PRT recipients for both maternal and fetal well-being.[19] With respect to the confirmation of pregnancy, follow-up by a multidisciplinary team composed of professionals in nephrology, endocrinology and obstetrics is essential with frequent checks.[20,21]

In accordance with the recommendations of the Consensus Conference on Reproductive Problems and Transplantation of 2005, all the patients included in our cohort strictly met the established criteria. These criteria include a minimum interval of 1 year since the renal transplant, optimal graft function (defined as serum creatinine levels less than 1.5 mg/dl) with minimal or no proteinuria, stability of immunosuppressive medication, the absence

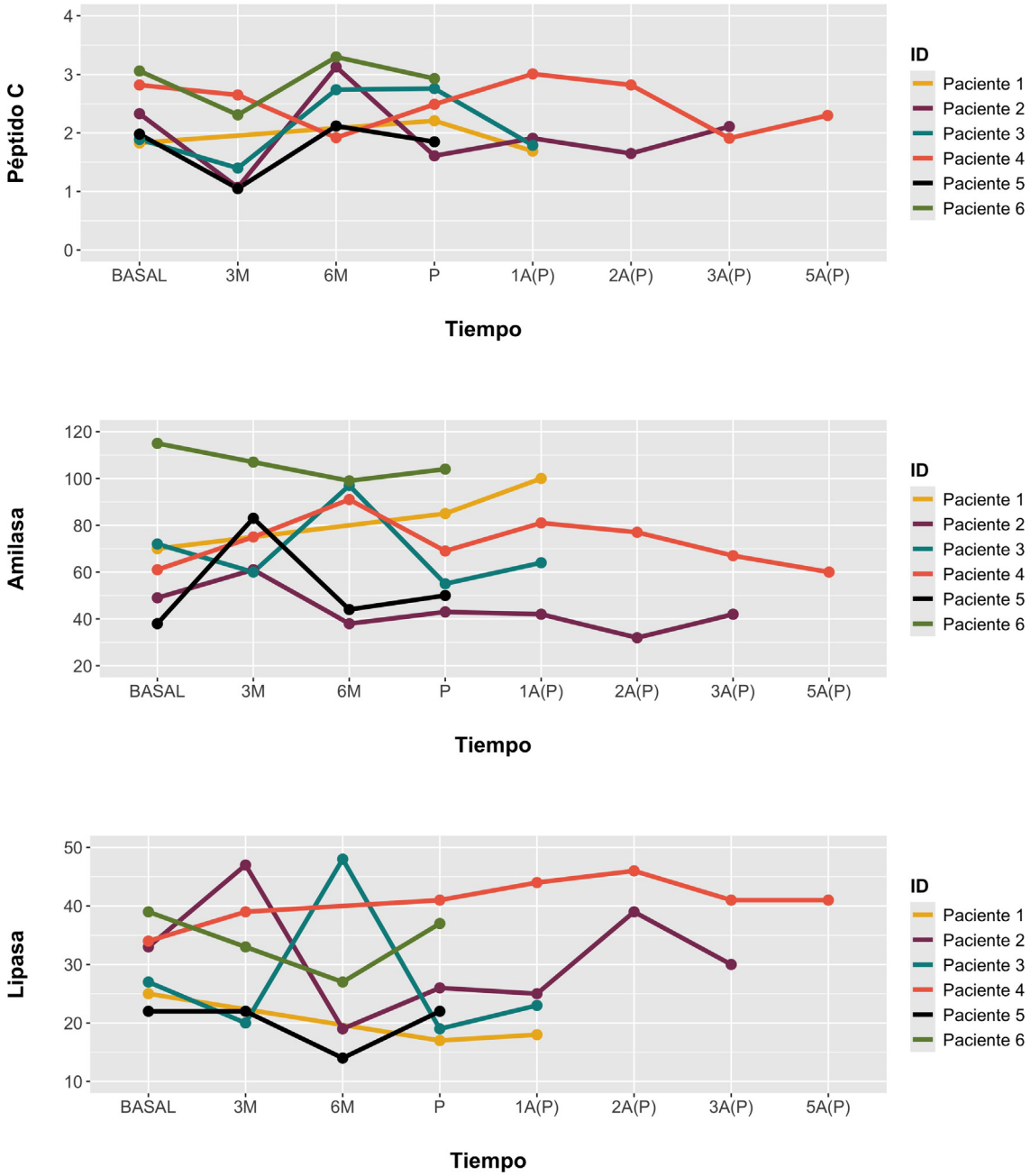


Figure 4. Changes in C-peptide (ng/mL), amylase (U/l) and lipase (U/l) levels.

of episodes of rejection and the absence of fetotoxic infections in the year prior to conception.[18]

In this series, the average time from transplantation to conception was 65.2 months, which was greater than that reported in previous studies, such as the 55 months reported by Bösmüller et al.,[22] the 28 months reported by Normand et al.,[23] and 52.8 months reported in the International Registry of Pregnancies in Transplant Recipients (TRPI).[24]

Similarly, we observed that the average age of the patients at the time of pregnancy was 38.8 years, which is comparable to the 37.9 years reported by Jain et al.[25] and slightly greater than the values reported in other studies, such as the 36.4 years observed by Punjala et al.[19] and 34.1 years documented by Normand et al.[23] These differences can be attributed to demographic, cultural and clinical factors specific to each cohort and highlight the importance of an individualized approach in the interpretation of the results.

Conception

Despite the indications that suggest an improvement in fertility after transplantation, the actual rate of conception in these women remains unknown because of the lack of data on the number of patients who tried to conceive without success. Infertility affects many women who receive transplants, leading them to seek alternatives such as IVF. However, these assisted reproductive techniques carry a higher risk of complications during pregnancy, such as preeclampsia, prematurity and fetal growth restriction.[26]

Although case reports[27,28] and some retrospective studies[29] have shown successful pregnancies after IVF in women who underwent PRT, the available evidence remains limited. In 2008, Fichez et al.[30] published a case of a successful pregnancy after IVF in a TRP recipient, followed by similar cases presented by Smyth et al.[31] in 2011 and Pietrzak et al.[32] in 2015, the latter in a woman who received a kidney transplant.

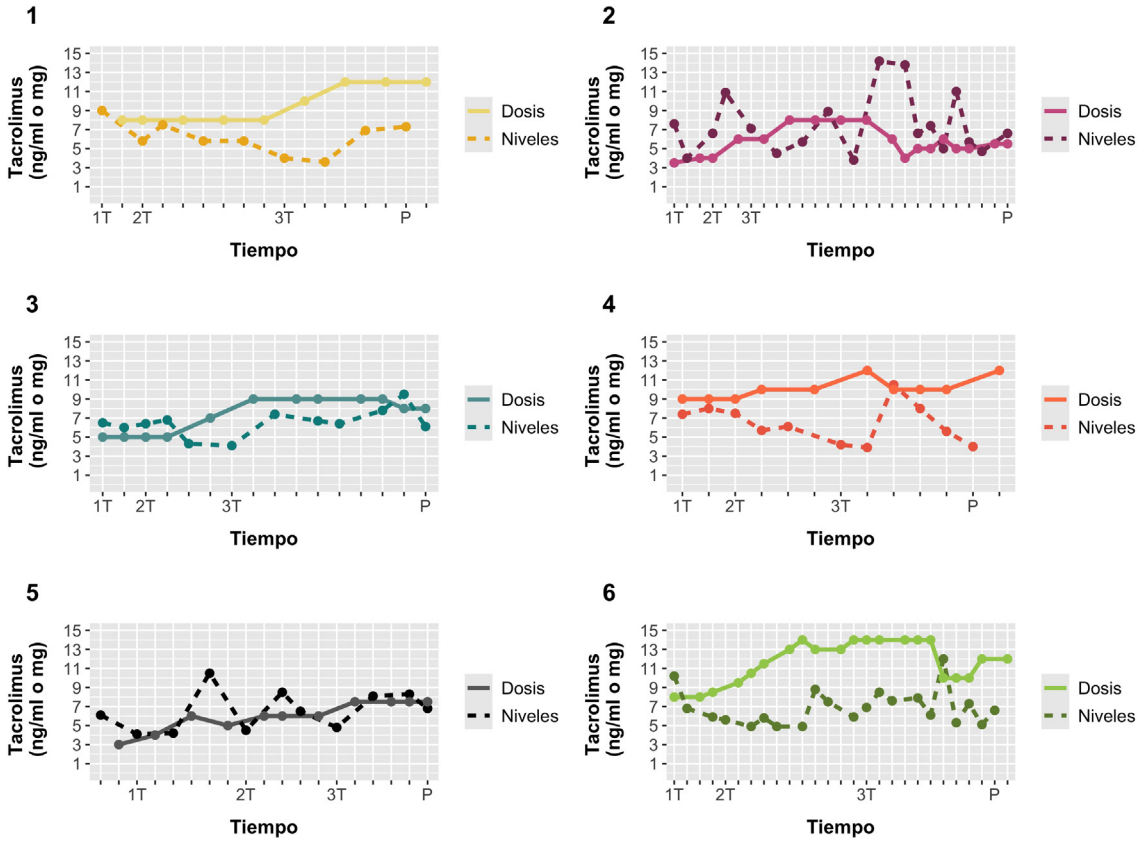


Figure 5. Levels of immunosuppressants and dose adjustment during pregnancy. Pharmacological levels (ng/mL) and the dose (mg) are reported.

Table 2
Characteristics of the newborns.

Patient (ID)	1	2	3	4	5	6
Gestational age (weeks)	33 + 3	36 + 2	37 + 5	31 + 0	38 + 2	36 + 2
Birth weight (g)	2,200	2,380	2,750	1,390	2,460	2,380
Sex	Female	Male	Male	Male	Female	Female
APGAR 1	6	6	10	10	7	10
APGAR 5	9	10	10	10	10	10

The results of our study reveal an interesting aspect related to conception through IVF in women receiving PRT, as 33% of the patients achieved pregnancy through this technique. These findings contrast with those of other studies in which the incidence of post-IVF pregnancies in this population was less frequent, such as in the study by Normand et al.[23] or in the 6 patients assessed by Bösmüller et al.,[22] in which no pregnancies were recorded after IVF among the patients included. However, in the study by Punjala et al.,[19] 8% of pregnancies were secondary to IVF, with good obstetric and maternal outcomes. However, these data could be overestimated and influenced by the study period, advances in assisted reproduction techniques or the health policies of each center.

Immunosuppressive therapy

In our study, all patients received immunosuppressive induction therapy with basiliximab, unlike other registries where thymoglobulin was more common, as evidenced in the study by Normand et al.[23] (90.9%) or in the study by Bösmüller et al.[22] (100%). With respect to maintenance treatment, although no standard regimen is available, the combination of prednisone, tacrolimus and mycophenolate mofetil/mycophenolic acid is widely used in these patients.

Since all the pregnancies were planned, preventive measures were implemented from the beginning of pregnancy. Folic acid supplementation was started, and treatment with low-dose aspirin was maintained to mitigate the risk of preeclampsia. In addition, a rigorous adjustment of the immunosuppressive therapy was performed according to the established guidelines. In the 4 patients who were treated with mycophenolate, it was replaced with azathioprine at least 6 weeks before conception, based on evidence showing increased risks of spontaneous abortions and birth defects, especially cardiovascular and cranial defects, associated with the use of mycophenolate during pregnancy.[26,33,34]

Notably, mTOR inhibitors, such as sirolimus and everolimus, have been shown to be teratogenic in animal studies, although the evidence in humans is limited. Therefore, the need to replace mTOR inhibitors before conception is recognized to prevent their possible teratogenic effect.[26,34] Similarly, in the 2 patients who were treated with mTOR inhibitors, this treatment was replaced with azathioprine.

On the other hand, steroids and calcineurin inhibitors were maintained throughout pregnancy because of their established safety profiles.[34–36] However, strict monitoring of immunosuppression is recommended to adjust the dose as necessary,[37] since increased doses may be required during pregnancy to maintain adequate serum levels because of physiological changes, such as the increased circulation volume or cytochrome P450 involvement [13.25].

Childbirth

In our study, 83.3% of deliveries (n = 5) were performed by cesarean section, mainly due to obstetric indications. This rate is

higher than that reported in other studies, such as 67% by Punjala et al.,[19] 72% by the TRPI annual report[24] and 73% by Normand et al.[23] In contrast, Bösmüller et al.[22] reported 100% cesarean sections, whereas in the study by Jain et al.,[25] all deliveries (100%) were vaginal.

Although the allograft is anatomically unlikely to suffer damage during vaginal delivery, an advanced maternal age could influence the higher prevalence of cesarean sections in RPT recipients. Notably, no maternal complications were recorded in any patients, suggesting that both options could be safe.

In terms of newborns, our cohort had a percentage of 100% live births, comparable to that of Jain et al. and higher than the 92.6% reported by Normand et al.[23] and Punjala et al.[19] This result is significantly higher than the value of 69% reported in the TRPI annual registry.[24]

Gestational age

In our cohort, 66% of the births were preterm, a rate comparable to those reported by Jain et al.[25] (66%) and Punjala et al.[19] (64%) but less than 80% of those reported by Normand et al.[23] and 76% of the annual registry of TRPI.[24] Highlighting these figures is important, since prematurity is associated with a wide variety of complications, such as respiratory distress syndrome, chronic lung disease, intestinal disorders, hearing and vision problems and neurological lesions.[38] However, the lack of long-term data generates uncertainty about possible future sequelae in children born prematurely to mothers who received a transplant.

In our cohort, 66.6% of the newborns had a low birth weight, and 16.7% had a very low birth weight; these results are similar to those reported by Punjala et al.[19] (60% with a low weight and 10% with a very low weight), Normand et al.[23] (70.8% with a low weight) and Bösmüller et al. (83.3% with a low weight and 16.7% with a very low weight).[22] In contrast, in the annual registry of TRPI,[24] 17% of newborns with a normal birth weight were documented. These findings suggest that prematurity was probably the main cause of the birth weight distribution. In fact, when weight was adjusted for gestational age, a marked decrease in the proportion of newborns with a birth weight less than the 10th percentile was observed.

Malformations

Most of the studies that investigated pregnancies in women receiving pancreas and kidney transplants do not mention congenital malformations but rather healthy newborns. However, some isolated cases have been documented over the years. For example, in 1989, a case of bilateral cataracts was documented in a newborn whose mother received treatment with cyclosporine during pregnancy.[39]

Between the mid-1980s and 1994, the International Registry of Pancreatic Transplantation[13] reported 2 cases of congenital malformations among 19 live newborns. In a more recent study conducted in France,[23] which included pregnancies in women receiving RPT between 1990 and 2013, 2 cases of congenital malformations were identified among 27 newborns. One of these cases involved ventriculomegaly, possibly related to a severe maternal pneumocystis infection, which resulted in spontaneous abortion at 26 weeks. The other case involved congenital cardiopathy, specifically a common arterial trunk with possible stenosis of the pulmonary artery, in a newborn who was exposed to sirolimus and mycophenolate mofetil during the first trimester of pregnancy.

The rates of congenital malformations vary between the different registries, from 3.8% in the annual registry of TRPI[24] to 7.4% in the study by Normand et al.[23] In contrast, in a case study similar to ours that was conducted by Bösmüller et al.,[22] which included 6 newborns, no congenital malformations were recorded. Malformations were also not recorded in the 3 newborns reported by Jain et al.[25] In our study, a case of mild malformation due to syndactyly was observed, but we were unable to exclude a familial predisposition.

Lactation

In recent years, the benefits of breastfeeding have been evident in the general population, especially for babies with a low birth weight and premature babies.[40] However, in the context of women receiving organ transplants, breastfeeding has been a topic of discussion and concern because of possible complications related to immunosuppressive therapy in newborns.

In our cohort, 4 newborns (66.7%) were exclusively breastfed, a proportion that is significantly higher than the 16% reported by Normand et al.[23] and 0% in the study by Bösmüller et al.[22] This difference in rates is probably due to concerns in the field of transplantation about the possible toxicity of immunosuppressive drugs during lactation.

Despite these concerns, recent studies have provided reassuring data suggesting that the excretion of immunosuppressive drugs through breast milk is lower than that through placental transfer during pregnancy.[41] Although the available evidence is limited, breastfeeding is recommended for female transplant recipients who take medications such as prednisone, azathioprine and tacrolimus. However, the use of drugs such as mycophenolic acid, sirolimus, everolimus and belatacept during lactation is not recommended because of insufficient information on possible adverse effects on infants.[42]

Evolution of the grafts

During pregnancy, a series of physiological changes can affect renal function and the immune response of the transplant recipient. Renal function can temporarily deteriorate during pregnancy and then recover to normal levels after delivery, unless prior renal involvement is present.[42]

Furthermore, the postpartum period is a stage of higher risk of graft rejection. This phenomenon can be attributed in part to the adaptation of the immune system during pregnancy, which includes immunological tolerance facilitated by the placenta.[25] However, the rapid elimination of the placenta after delivery can cause rapid loss of this immunological tolerance.

In the context of PRT, an evaluation of the effects on both grafts and the incidence of rejection during pregnancy and the postpartum period is essential. In our series, patients experienced 100% renal and pancreatic graft survival both during pregnancy and during the follow-up period. In addition, none of them presented rejection during pregnancy or the following year. Importantly, all of them had a previous negative laboratory screen, a result that was maintained in subsequent immunological controls.

With respect to pancreatic function, both blood glucose levels and HbA1c levels remained stable throughout follow-up in all patients, without the need to restart insulin treatment in any case.

In comparison, studies such as that by Normand et al.[23] revealed that 96% of renal grafts and 100% of pancreatic grafts survived at 1 year, with reductions to 72.7 and 68.7%, respectively, observed at 84 months after conception. In other studies, such as that by Jain et al.,[25] renal and pancreatic function remained stable during pregnancy and follow-up (up to 42 months postpartum). However, in the cases reported by Punjala et al.,[19] renal graft function was lost in 2 patients (15.4%), 1 at 1 year and the other at 3 years, as well as the function of a pancreatic graft (7.7%) at 2 years after pregnancy.

Conclusions

In our experience, pregnancy in patients with PRT has a favorable course.

The inherent complexity of this situation lies in the need to address a variety of factors, including preconception counseling, immunosuppressive treatment adjustment and multidisciplinary follow-up among professionals in nephrology, endocrinology and obstetrics. Close collaboration between clinicians in these specialties is essential to ensure the success of pregnancy and maternal–fetal health. While nephrologists play a crucial role in the management of renal function and immunosuppression, obstetricians monitor the course of pregnancy and address possible obstetric complications, ensuring safe delivery. Moreover, endocrinologists optimize metabolic and endocrine control, ensuring proper management of diabetes and other conditions associated with transplantation.

Despite advances in obstetric, perinatal and nephrological care, questions still remain about how pregnancy can affect both the mother and the fetus, as well as the repercussions on both grafts, especially in patients who receive a combined pancreas and kidney transplant, where the clinical experience remains limited.

Limitations

Several limitations should be considered when the results of this study are interpreted. First, the main limitation is the small size of the cohort of patients included in this analysis.

Another important limitation is the duration of patient follow-up. Although data were collected throughout the gestational period and up to 1 year after delivery, a longer follow-up period would have allowed a more complete evaluation of the long-term results, including graft survival and the incidence of subsequent complications.

In summary, although this study provides valuable information on pregnancy in patients after PRT, these limitations should be considered when the results are interpreted and generalized. Prospective and multicenter studies with longer-term follow-up are needed to validate and expand the findings of this study and improve the understanding of the effects of pregnancy on this patient population.

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Declaration of competing interest

The authors declare that they have no conflicts of interest.

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