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Pregnancy in renal transplant patients: Renal function markers and maternal–fetal outcomes

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ABSTRACT

Objectives: We aimed to evaluate laboratory markers in women who got pregnant after renal transplantation.
Study design: Cross-sectional prospective study.
Main outcome measures: Renal function parameters and maternal and fetal data were assessed in renal transplant recipients.
Results: Forty-three women who got pregnant after renal transplantation (mean age, 28.5 years; mean gestational age, 35.6 weeks) were included. Most patients (53.5%) received a renal transplant from a deceased donor. Podocyturia was not significantly correlated with other renal function markers. Mean period from transplantation to pregnancy was approximately 5 years; this period was not associated with obstetric complications or changes in renal markers. A gradual increase was observed in the following parameters during pregnancy and puerperium: serum creatinine levels ($P < 0.001$), proteinuria ($P < 0.001$), urinary protein/creatinine ratio ($P < 0.001$), and albumin/creatinine ratio ($P < 0.001$). The sensitivity and specificity of protein/creatinine ratio in predicting preeclampsia were high (96.0% and 94.0%, respectively). Elevated serum creatinine levels, urinary albumin/creatinine ratio, and retinol-binding protein levels in the third trimester were associated with prematurity ($P < 0.001$). Preeclampsia was the main cause of renal function decline at the end of pregnancy (65.0% of cases). Approximately four (9.5%) pregnant women presented with premature rupture of membranes and 18 (42.0%) with a urinary tract infection.
Conclusions: Proteinuria, urinary protein/creatinine ratio, and retinol-binding protein levels were elevated in patients with preeclampsia. Using these markers to assess renal function during pregnancy may be clinically useful for detecting and monitoring renal injury in renal transplant recipients.

1. Introduction

The possibility of curing a disease by simply replacing the injured organ was no longer a fiction by the early 20th century. Advances in surgical techniques and immunosuppressive therapy in recent decades have increased the effectiveness of organ transplantation in treating end-stage organ failure. In addition to the gradual improvement in graft and patient survival and quality of life, the reproductive function is often restored after transplantation [1]. Renal, endocrine, and sexual functions rapidly return to normal after successful renal transplantation [2]. However, a few patients develop acute rejection, dysfunction, or allograft loss, and these conditions are unpredictable and may be related to pregnancy after transplantation. Therefore, it is important to diagnose renal injury at an early stage.

Chronic nephropathy of the graft, chronic rejection, and other conditions, including nephrotoxicity of immunosuppressive drugs, culminate in glomerulosclerosis and tubular atrophy/interstitial fibrosis [3]. Research is ongoing to identify reliable non-invasive biomarkers of acute and chronic renal injury, thereby enabling the diagnosis of renal injury in its early stages and use of these markers for renal disease

Abbreviations: ACR, albumin/creatinine ratio; BMI, body mass index; PCR, protein/creatinine ratio; RBP, retinol-binding protein

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staging according clinical severity, prediction of disease outcomes, and monitoring of response to therapeutic interventions.

2. Methods

2.1. Patients

This study was conducted at the outpatient Hypertension and Nephropathy Clinic of the Federal University of São Paulo, Brazil, from August 2014 to March 2016. The sample included pregnant renal transplant recipients with singleton gestations. Renal transplant recipients with kidney failure and patients on dialysis were excluded. This study was approved by the Research Ethics Committee of our institution, and all patients signed an informed consent form.

2.2. Evaluation

Blood samples were collected to determine serum creatinine (by alkaline picrate method) and serum urea levels (by enzymatic method). Mid-stream urine samples were collected to determine proteinuria, including retinol-binding protein (RBP; by enzyme immunoassay using monoclonal antibodies considered elevated when above 0.4 mg/L) [4]; the capture monoclonal antibody (A8P3) was adsorbed to microtiter plate wells (Nunc A/C, Roskildo, Denmark) at the concentration of 10 mg/mL in binding buffer (100 mL/well). After incubation for 16 h at 4 °C, the wells were washed three times with wash buffer. Urine and diluted standards were then added in assay buffer (50 mL) and biotin-labeled E9P6 monoclonal antibody (50 mL). After incubation for 2 h at 37 °C and a new wash cycle, streptavidin peroxidase (Amersham International plc, Amersham, UK) was added and incubated for one hour at 37 °C. After four washes, the colorimetric reagent was added. After 30 min of incubation at room temperature, the reaction was blocked by the addition of 25 mL of 1.0 NH_2SO_4. The absorbance (492 nm) was then read on a plate reader (Bio-tek, VT, USA). Concentrations in the samples were calculated using a standard curve (normal human plasma, Behring, used as reference material) using nonlinear regression, 3rd degree polynomial, for the calculations), albuminuria (by immunoturbidimetry being considered as microalbuminuria values between 30 and 300 mg/L and macroalbuminuria, above that level) [5], albumin/creatinine ratio (ACR; by immunoturbidimetry, the cutoff was 30 mg/g) [6], protein/creatinine ratio (PCR; by the alkaline picrate colorimetric method was lower than 0.3 g/g) [7], and podocyturia (by indirect immunofluorescence) [8].

2.3. Statistical analysis

Statistical analyses of all the collected data was initially performed descriptively using means, medians, minimum and maximum values, standard deviations, absolute and relative frequencies (percentage), and bar graphs.

The inferential analysis used to confirm or refute the evidence obtained in the descriptive analysis included the Friedman's test, non-parametric analysis of ordinal data with repeated measures, and Cochran's Q test for comparing renal markers over time. Pearson's chi-square test, Fisher's exact test or its extension, and linear-by-linear association test were used to compare sociodemographic characteristics and results of physical examinations and laboratory tests. The significance level alpha was set at 5% for the results obtained using the inferential analysis. Statistical analyses were performed using the R software version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Tables 1 and 2 summarize the patients' characteristics, and Fig. 1 the profile of renal biomarkers in patients with and without

Table 1
General characteristics of the pregnant women.

Maternal age (years)	n	43	
	Mean	28.5	
	Median	30.0	
	Standard deviation	5.5	
Ethnicity	Caucasian	31	72.0%
	Black	5	12%
	Mixed	7	16.0%
	Total	43	100.0%
Classification according to body mass index	Malnutrition	1	2.5%
	Eutrophy	16	37.0%
	Overweight	15	35.0%
	Obesity	11	25.5%
Etiology			
Glomerulopathy	23	53.5%	
Hypertension	3	7.0%	
Urinary tract infection	2	4.5%	
Vesicoureteral reflux	2	4.5%	
Diabetes mellitus	1	2.5%	
Unknown	12	28.0%	
Total	43	100.0%	
Type of kidney donor			
Living	20	46.5%	
Deceased	23	53.5%	
Total	43	100.0%	
Period between renal transplantation and pregnancy (years)			
N	43		
Mean	5.0		
Median	4.0		
Standard deviation	4.0		

Table 2
Characteristics of delivery and comorbidities in pregnant women.

Type of delivery	Normal	13	30.0%
	Forceps	2	5.0%
	Cesarean	28	65.0%
	Total	43	100.0%
Preeclampsia	Yes	28	65.0%
	No	15	35.5%
	Total	43	100.0%
Chronic hypertension	Yes	21	47.5%
	No	22	52.5%
	Total	43	100.0%
Anemia	Yes	26	60.5%
	No	17	39.5%
	Total	43	100.0%
Diabetes mellitus	Yes	4	9.5%
	No	39	90.5%
	Total	43	100.0%
Premature rupture of membranes	Yes	4	9.5%
	No	39	90.5%
	Total	43	100.0%
Blood transfusion	Yes	2	4.5%
	No	41	95.5%
	Total	43	100.0%
Urinary tract infection	Yes	18	42.0%
	No	25	58.0%
	Total	43	100.0%
Prematurity	Yes	22	51.0%
	No	21	50.0%
	Total	43	100.0%
Adequate weight for age	AGA*	30	69.5%
	SGA**	13	30.5%
	Total	43	100.0%

* Adequate for gestational age.
** Small for gestational age.

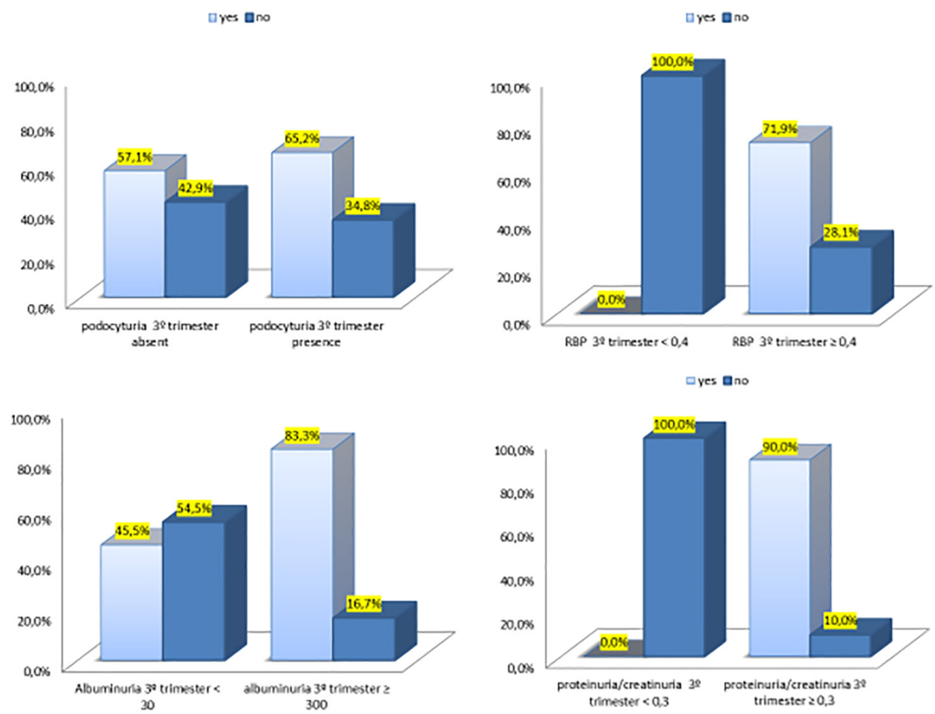

Fig. 1. Percentage of patients with data of patients with (1st bars) vs without preeclampsia (2nd bars) after renal transplantation.

Table 3
Primary analysis of the functional renal markers, according to the moment in time.

	Mean	Median	Minimum	Maximum	Standard deviation	p[a]
Serum creatinine						
2nd trimester	1.11	0.87	0.57	4.20	0.73	< 0.001
3rd trimester	1.44	1.20	0.60	4.40	0.83	
After childbirth	1.35	1.10	0.60	4.10	0.71	
Proteinuria						
2nd trimester	0.18	0.00	0.00	4.00	0.63	< 0.001
3rd trimester	0.91	0.55	0.00	4.40	1.17	
After childbirth	0.19	0.00	0.00	1.60	0.42	
Podocyturia						
2nd trimester	814.14	585.10	0.00	3568.38	1044.62	0.529
3rd trimester	260.03	75.67	0.00	2280.98	470.94	
After childbirth	304.06	351.00	0.00	875.53	265.62	
Albuminuria/creatininuria						
2nd trimester	69.31	14.30	0.30	613.70	157.21	< 0.001
3rd trimester	268.45	87.00	0.30	2199.00	458.36	
After childbirth	122.14	77.50	19.00	375.00	115.93	
Creatininuria						
2nd trimester	83.76	87.90	5.50	173.40	46.74	0.441
3rd trimester	98.63	93.42	16.80	244.40	64.11	
After childbirth	125.91	92.40	9.60	307.90	88.14	
RBP ur[*]						
2nd trimester	8.99	0.74	0.17	59.74	19.82	0.135
3rd trimester	12.08	1.81	0.11	56.60	17.93	
After childbirth	13.35	8.59	0.04	60.00	17.49	
Proteinuria/creatininuria						
2nd trimester	1.57	0.30	0.10	11.00	2.46	< 0.001
3rd trimester	5.81	4.60	0.12	19.10	5.85	
After childbirth	2.37	0.55	0.10	14.00	3.29	

[a] Friedman.
* Urinary retinol-binding protein.

preeclampsia after renal transplantation. Primary analysis of the functional renal markers, according to the moment in time were in Table 3. Serum creatinine level ($P < 0.001$), proteinuria ($P < 0.001$), and urinary PCR ($P < 0.001$) gradually increased during pregnancy and decreased after childbirth, in contrast to ACR, which was high throughout the pregnancy and remained elevated even after childbirth ($P < 0.001$), suggesting that renal graft dysfunction persisted after pregnancy. The sensitivity and specificity of PCR in predicting preeclampsia were high in the study patients (96.0% and 94.0%, respectively). Podocyturia was not significantly correlated with renal function markers or primary maternal and fetal outcomes (preeclampsia, prematurity, adequate weight for age, and low birth weight). Increased ACR, serum creatinine level, and urinary RBP level in the third trimester were associated with prematurity.

3.1. Clinical data

The age of the study patients was 17–39 years. The mean period from transplantation to pregnancy was approximately 5 (range, 1–15) years. The number of obstetric complications, namely preeclampsia, prematurity, adequate weight for age, and low birth weight, related to pregnancy after transplantation did not increase in the study period. The mean gestational age at delivery was 35.6 weeks; the mean weight at birth was 2358.5 g. Several etiologies of renal failure before transplantation were identified in the study patients, with a predominance of glomerulopathy (53.5%) and chronic hypertension (7.0%). Most of the evaluated pregnant women received an organ from a deceased donor (53.5%).

4. Discussion

Pregnancy causes significant changes in renal function. One of the most notable changes is the increase in renal plasma flow with a subsequent increase in the glomerular filtration rate by approximately 50%. However, there is controversy regarding the effect of pregnancy on glomerular disease progression and graft survival in patients with glomerular impairment. This adaptive response does not appear to be the same among pregnant transplant recipients. Moreover, morphological and functional changes may occur, and the risk of perinatal mortality and morbidity is increased [9].

The number of maternal and fetal outcomes, namely preeclampsia, prematurity, adequate weight for age, and low birth weight, related to pregnancy after transplantation did not increase in the study period. However, analysis of allograft acceptance in the first year postoperatively indicated a decline in renal function. The cause of allograft dysfunction is still uncertain, but this complication has been suggested to be caused by acute and chronic rejection of the graft in women who become pregnant [10]. Some studies have reported a reduction in the serum levels of immunosuppressive drugs during pregnancy, and some guidelines have recommended more frequent monitoring of these medications during pregnancy [11]. The instability of the therapeutic doses of immunosuppressive drugs was probably the cause of allograft dysfunction in patients who became pregnant in the first year of transplantation in the present study.

In our patients, deceased donor renal transplant was the most common type of transplant, and it is noteworthy that this situation is ideal because it avoids the risk of complications related to surgery in healthy donors and the donors do not have to live with only one kidney [12].

The mean body mass index (BMI) was 26.8 (range, 17.3–35.0) kg/m^2. Considering the BMI categories, only 37.0% of patients had eutrophic BMI and most patients were overweight (35.0%) or obese (25.0%). The use of medications, such as corticosteroids, may have contributed to > 50% of patients being overweight or obese; however, the trend for a gradual increase in BMI in the Brazilian population in recent years needs to be considered. The implications of being overweight and obese on pregnancy are presently being studied because of the short- and long-term consequences [13].

Anemia is a common consequence of chronic nephropathy because of the reduced production of erythropoietin [14]. The anemia rate in the study population was 60.5%. Among puerperal women, 4.5% required blood transfusion in the first 2 days after delivery. An alternative strategy for treating anemia is using human recombinant erythropoietin, as reported by Van Biesen in 2005 [15].

The unique characteristics exhibited by transplant recipients make urinary tract infection a feared condition that requires constant prophylaxis during pregnancy. In addition, the anatomical and functional changes that occur in the urinary system of pregnant women increase their susceptibility to complications during pregnancy [16]. In our patients, 42.0% of the patients were diagnosed with urinary infections, and this percentage is similar to that reported in another study [17]. A greater renal function decline due to urinary tract infection has also been reported [18].

Preeclampsia was the most common obstetric complication, with 65.0% of our patients having this condition; however, this rate is similar to that reported in other studies [19]. Several conditions predispose pregnant women to preeclampsia, including diabetes, vasculopathy, and nephropathy [20]. Several of these conditions have been diagnosed in women who have undergone transplantation. Therefore, because preeclampsia causes high maternal and perinatal morbidity, we believe that these patients should be considered more susceptible to this disease. Therefore, preeclampsia should be carefully screened for in renal transplant recipients because its diagnosis is more difficult in this population, most of which has chronic hypertension and proteinuria.

Prematurity is responsible for high fetal morbidity and mortality rates and affects the quality of life because of potential immediate or late sequelae. Therefore, the implementation of public policies that provide care to neonates is essential. The reported rate of prematurity varies from 50% [21] to 80% [22]; as previously mentioned, fetal outcomes are closely associated with the degree of renal dysfunction, severe hypertension, and proteinuria. In our study population, 51.0% of the 43 births were preterm. With regard to adequate birth weight for gestational age, 30.5% of newborns were small for the gestational age, which reflected fetal growth restriction. However, prematurity was not directly correlated with the degree of renal dysfunction but rather with the presence of other maternal comorbidities, such as hypertension and proteinuria.

The analysis of glomerular filtration function of the allograft in the 43 pregnancies indicated that 53.0% of the study population had some degree of dysfunction (mean serum creatinine level, 1.44 mg/dL) at the end of pregnancy. The renal filtration rate is reported to be decreased during the pregnancy–puerperium cycle. However, this decrease does not have a negative effect on renal graft or patient survival [9]. In our patients, preeclampsia was the main cause of this functional deterioration (65.0% of cases).

In addition to serum creatinine levels, proteinuria was an important non-invasive marker in the present study. Proteinuria gradually increased during pregnancy and decreased after delivery.

PCR is one of the available parameters to assess proteinuria in spot urine samples and is an alternative to the 24 h measurement of proteinuria in urine. PCR is successfully used to evaluate renal transplant recipients because it is quick, easy, and not affected by variations in the urine concentration [23], especially in severe cases, in which this information is urgently required [24]. The sensitivity and specificity of PCR in predicting changes equivalent to proteinuria of 300 mg/24 h in pregnant women with suspected preeclampsia were 90%–99% and 33%–65%, respectively [25]. The sensitivity and specificity of PCR in predicting preeclampsia in this study population were high (96.0% and 94.0%, respectively). Reportedly, high proteinuria does not correlate with the severity of preeclampsia and does not occur in 10% of cases [26,27]. However, elevated proteinuria using PCR in women with preeclampsia is associated with a higher probability of adverse maternal outcomes [28]. In cases in which no information is available on the presence or absence of proteinuria in early pregnancy, the distinction between an underlying primary renal disease and preeclampsia may be very difficult. The presence of systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg, diagnosed for the first time after the 20th week of gestation in those patients who had proteinuria since the beginning of pregnancy, a rise three times higher than the initial values was considered preeclampsia.

Albuminuria is a more sensitive marker than proteinuria, and values > 300 mg/L (macroalbuminuria) indicate damage to the glomerular basement membrane. In our study population, an increase was observed in urinary ACR during pregnancy, and this marker remained elevated even after childbirth, suggesting graft function deterioration after pregnancy.

RBP was chosen as one of the biomarkers because it a well known and available marker in our service and it was a useful tool in the renal evaluation of pregnant women (not submitted to renal transplantation) in previous studies of our laboratory [29] as well as in patients with glomerulopathies [30] and renal grafts [31]. RBP is a good tubular function biomarker, as others like beta2-microglobulin and NGAL. RBP, recently classified as an adipokine, is primarily synthetized in the liver and used as a marker of obesity, inflammation, and insulin resistance. RBP4, the plasma form of RBP, is decreased in pregnant women under acute stress conditions, including sepsis and pyelonephritis [32]. Notably, RBP4 levels are increased in women with preeclampsia, suggesting that RBP is involved in the pathophysiology of vascular dysfunction in preeclampsia [33]. RBP is continuously produced, and its stability in normal urinary pH is an advantage for assessing tubulointerstitial dysfunction. In the present study, the urinary excretion of RBP was increased during pregnancy and was particularly elevated in the second and third trimesters. The urinary RBP levels were not correlated with the period from transplantation to pregnancy, prematurity, or weight at birth. In addition to proteinuria, creatinuria, and PCR, RBP level was elevated in preeclampsia. No study till date has assessed urinary RBP levels in pregnant transplant recipients with preeclampsia; however, our findings indicated the occurrence of proximal tubular reabsorption dysfunction in this group. Whether the elevation of urinary RBP level is due to preeclampsia (which is accentuated in transplanted patients), chronic dysfunction of the allograft, or both is unknown.

Studies conducted in our department with non-pregnant transplant recipients of both sexes have demonstrated that elevated urinary RBP levels indicate chronic allograft rejection and that the measurement of this parameter is useful in clinical practice [34].

Podocyturia is another diagnostic parameter assessed in the present study, which is still understudied, especially in the context of renal transplantation. In recent years, it has been proposed as a laboratory marker in glomerular diseases. Podocyturia may be present in healthy individuals and in patients with glomerulopathy and is significantly more intense in the latter, especially in cases in which the disease is active [35].

We found no relevant contribution of the analysis of podocyturia in pregnant transplant recipients or a threshold for considering podocyturia as abnormal in this population. Additional research is necessary to evaluate podocyturia in renal transplant recipients and determine whether its potential correlation with proteinuria may be affected by differences in tubular absorption, hemodynamic conditions, and gestational age [36]. A study reported that the absence of podocyturia in normal pregnant women might indicate the absence of kidney injury, whereas its presence might indicate active glomerulopathy [37].

Podocyte injury may occur in pregnant transplant recipients, and its assessment may be useful for diagnosing, preventing, and monitoring glomerular disease.

Other evaluated urinary laboratory markers are useful for detecting allograft dysfunction during pregnancy. The advantage of PCR and ACR is the low cost, ease of use, and agility. These characteristics suggest that such methods should be included in the investigation of renal dysfunction in renal transplant recipients. Urinary RBP levels and podocyturia may be elevated in preeclampsia; however, the role of these markers has not been completely clarified in pregnant transplant patients.

Preeclampsia is an important cause of glomerulopathy worldwide and may be a clinical marker of increased risk of end-stage renal disease [38]. Filtration and glomerular function are affected in preeclampsia [39,40] and probably do not completely recover after childbirth [41]. In this context, early diagnosis of glomerular disorders, including after preeclampsia, in pregnancy using appropriate laboratory tests may allow immediate treatment and improvement of prognosis in the affected women. Our results indicated that microalbuminuria; urinary PCR, ACR, and RBP levels; and analysis of podocyturia might contribute to the diagnosis of glomerular dysfunction during pregnancy.

We emphasize that the evaluation of graft function in pregnancy should be routinely performed, even in asymptomatic patients, by a multidisciplinary team, i.e., an obstetrician and a nephrologist because other complications, including graft rejection, recurrence of previous glomerular diseases, ureteral obstruction, and urinary tract infection, may be the underlying causes of the dysfunction.

The two most important markers related to maternal–fetal prognosis are the degree of renal dysfunction and hypertension at the time of conception. In the absence of severe or difficult-to-control hypertension, moderate or severe allograft dysfunction, advanced diabetic nephropathy, or lupus nephritis, the rates of maternal and fetal complications are low. Moreover, pregnancy does not appear to accelerate the loss of kidney function in patients with mild dysfunction, partly because of the lower risk of hypertensive complications, in contrast to that in women with moderate and severe dysfunction for whom the maternal and fetal risks are drastically increased.

Taking these findings into consideration, the current trend is to not contraindicate conception in female renal transplant recipients who do not present major loss of renal function because there is a reasonable expectation of successful gestation and little likelihood of disease worsening because of pregnancy. Several complications may occur in women with moderate or severe renal dysfunction who are at a high risk of progression to end-stage renal disease despite care by health professionals. Moreover, fertility declines with disease progression and the chances of conception decrease.

Conception should be planned in cases in which clinical and/or renal disease-related complications are controlled. Therefore, these patients should begin to be monitored in the preconception phase by a nephrology team.

Adequate clinical and obstetric decisions, in combination with individualized care based on a good clinician–patient relationship, can lead to better perinatal outcomes in this group of patients.

Declarations of interest

None.

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