Pregnancy after kidney transplantation: high rates of maternal complications

Gestação após o transplante renal: alto índice de complicações maternas

Abstract

Introduction: Women regain fertility a few time after renal transplantation. However, viability of pregnancy and maternal complications are still unclear. Objective: To describe the outcomes of pregnancies in kidney transplanted patients, focusing on maternal complications. Methods: Retrospective study of pregnancies in kidney transplanted patients between 2004 and 2014, followed up 12 months after delivery. Each pregnancy was considered an event. Results: There were 53 pregnancies in 36 patients. Mean age was 28 ± 5 years. Pregnancy occurred 4.4 ± 3.0 years post-transplant. Immunosuppression before conception was tacrolimus, azathioprine, and prednisone in 74% of the cases. There were 15% miscarriages in the 1st trimester and 8% in 2nd trimester. In 41% of the cases, it was necessary to induce labor. From all births, 22% were premature and 17% very premature. There were 5% stillbirths and 5% of neonatal deaths. De novo proteinuria occurred in 60%, urinary tract infection in 23%, preeclampsia in 11%, acute rejection in 6%, and graft loss in 2% of the cases. It was observed a significant increase in creatinine at preconception comparing to 3rd trimester and follow-up (1.17 vs. 1.46 vs. 1.59 mg/dL, p < 0.001). Conclusion: Although the sample is limited, the number of miscarriages was higher than in the general population, with high rates of maternal complications. Sustained increase of creatinine suggests increased risk of graft loss in long-term.

Keywords: abortion; graft rejection; kidney transplantation; pre-eclampsia; pregnancy.

Resumo

Introdução: Após o transplante renal, as mulheres recuperam a fertilidade em pouco tempo. Entretanto, a viabilidade da gestação e as complicações maternas da gravidez ainda são objeto de estudo. Objetivo: Descrever a evolução da gestação após o transplante renal, com foco principal nas complicações maternas. Métodos: Estudo retrospectivo de casos de gravidez ocorridos entre 2004 e 2014 em pacientes transplantadas renais, com seguimento de 12 meses após o parto. Cada gravidez foi considerada um evento. Resultados: Houve 53 gestações em 36 pacientes. A média de idade foi de 28 ± 5 anos. Gravidez ocorreu 4,4 ± 3 anos após o transplante renais. Imunossupressão preconcepção era composta de tacrolimo, azatioprina e prednisona em 74% dos casos. Houve 15% de aborto no 1º trimestre e 8% no 2º trimestre. Em 41% dos casos, foi necessário induzir o parto. De todos os nascimentos, 22% foram prematuros e 17% muito prematuros. Houve 5% de mortes neonatais. Proteinúria de novo ocorreu em 60%, infecção do trato urinário em 23%, pré-eclâmpsia em 11%, rejeição aguda em 6% e perda do enxerto em 2% dos casos. Foi observada elevação significante da creatinina quando comparados período preconcepção, 3º trimestre e pós-12 meses de seguimento (média de 1,17 vs. 1,46 vs. 1,59 mg/dL, p < 0,001). Conclusão: Os resultados demonstram taxa de aborto maior que na população em geral, com altas taxas de complicações maternas. Aumento sustentado da creatinina sugere aumento do risco de perda do enxerto em longo prazo.

Palavras-chave: aborto; gravidez; pré-eclâmpsia; rejeição de enxerto; transplante de rim.

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INTRODUCTION
Achieving maternity can still be a challenge for women with chronic kidney disease (CKD). As renal disease progresses, sexual interest and fertility decline. One of the benefits of kidney transplantation is the reversion of gonadal dysfunction and the restoration of fertility. Approximately 2% of female recipients of a kidney transplant at child-bearing age become pregnant during follow-up. Although there is an undoubtedly positive aspect of kidney transplantation, these patients constitute a special high-risk group regarding pregnancy, with potentially life-threatening maternal and fetal complications.

Data from a recent study, from the United Kingdom national cohort, suggest that the majority of renal transplant recipients can achieve successful pregnancies, although adverse events are common. However, this study evaluated patients in different transplant centers and under different practices during follow-up. There is still a reduced number of studies analysing large cohorts with similar standards of obstetric and nephrology care. The aim of this study was to collect information about pregnancy outcomes among renal transplant recipients under similar care regarding obstetric follow-up and transplant conditions.

METHODS
This was an observational retrospective, single-center study. The study design was reviewed and approved by local Ethics Committee. Eligible patients were all the renal transplant recipients that became pregnant between 2004 and 2014. Since all renal transplant recipients keep their follow-up in the same institution along their lives after transplantation, and all tests are performed in a single central laboratory, patients were actively selected by retrospectively identifying a positive β-human chorionic gonadotropin test during the studied period from the laboratory data bank. Data regarding fetal birthweight was not available for this analysis.

The main outcome was the occurrence of any maternal complication. Information regarding the preconception period (3 to 12 months prior to conception), each trimester of the pregnancy and short-term follow-up (12 months after delivery) was collected from the medical records maintained by the institution. For this analysis, each pregnancy was considered an event.

Demographic, clinical and laboratory parameters were described. All women received continuous antimicrobial prophylaxis with cotrimoxazol during pregnancy and follow-up. Urine samples were collected for culture in each medical visit, and all bacteriuria (> 10⁵ CFU/mL), even asymptomatic, was treated appropriately. Proteinuria was evaluated in isolated urine samples, and the result was expressed as g/L. Neither quantification of 24h-protein excretion nor urinary protein/urinary creatinine ratio were available for this present analysis. Glomerular filtration rate was estimated by CKD-EPI equation. Preeclampsia was defined according to American College of Obstetricians and Gynecologists guidelines 2013.

Quantitative variables were expressed as mean and standard deviation. Evolution of renal function (estimated by serum creatinine) and proteinuria over time was assessed by repeated measures analysis method. Categorical variables were expressed as number and percentage, Chi-square test was used for comparison. For all tests, statistical significance is considered if p-value < 0.05, 95% CI.

RESULTS
DEMOGRAPHIC CHARACTERISTICS
Fifty-three pregnancies occurred in 36 renal transplant recipients. Twelve patients had more than one pregnancy during the respective period. Demographic characteristics are summarized in Table 1. Regarding baseline immunosuppression, four women were in use of tacrolimus, prednisone and mycophenolate before conception. One of them was switched to azathioprine at diagnosis of pregnancy. The other three, occurring before 2012 (time of publishing the FDA Mycophenolate REMS program and wider awareness of the issues regarding MPA/MMF and embryotoxicity), continued on this therapy during pregnancy, due to the high immunological risk and late diagnosis of pregnancy.

PREGNANCY EVENTS AND NEONATAL OUTCOMES
There was no provoked abortion. There were nine miscarriages (one at 7 weeks, two at 8 weeks, one at 9 weeks, four at 10 weeks and one at 13 weeks) and three stillbirths (one at 20 weeks, two at 22 weeks). Two out of three pregnancies among women who continued the use of mycophenolate resulted in miscarriages (at the 8th and the 10th gestational week, respectively).
<table>
<thead>
<tr>
<th>Variable</th>
<th>n = 53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at transplantation, years</td>
<td>23 ± 6 (12 - 33)</td>
</tr>
<tr>
<td>&lt; 20 years</td>
<td>6 (11)</td>
</tr>
<tr>
<td>20 - 34 years</td>
<td>41 (77)</td>
</tr>
<tr>
<td>≥ 35 years</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Mean age at conception, years</td>
<td>28 ± 5 (17 - 40)</td>
</tr>
<tr>
<td>&lt; 20 years</td>
<td>6 (11)</td>
</tr>
<tr>
<td>20 - 34 years</td>
<td>41 (77)</td>
</tr>
<tr>
<td>≥ 35 years</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Melanodermic</td>
<td>27 (51)</td>
</tr>
<tr>
<td>Non-melanodermic</td>
<td>26 (49)</td>
</tr>
<tr>
<td>Formal educational level, n (%)</td>
<td></td>
</tr>
<tr>
<td>Illiteracy</td>
<td>1 (2)</td>
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<tr>
<td>Elementary</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Secondary</td>
<td>36 (68)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Non available</td>
<td>7 (13)</td>
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<tr>
<td>Cause of end-stage renal disease, n (%)</td>
<td></td>
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<tr>
<td>Diabetes Mellitus</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Glomerulopathy</td>
<td>18 (34)</td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (57)</td>
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<tr>
<td>Chronic interstitial nephritis</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Oligomeganeferonia</td>
<td>1 (2)</td>
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<tr>
<td>Previous treatment, n (%)</td>
<td></td>
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<tr>
<td>Hemodialysis</td>
<td>50 (94)</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>2 (4)</td>
</tr>
<tr>
<td>None</td>
<td>1 (2)</td>
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<tr>
<td>Time on dialysis, months</td>
<td>28 ± 26 (0 - 144)</td>
</tr>
<tr>
<td>Up to 36 months</td>
<td>39 (74)</td>
</tr>
<tr>
<td>More than 36 months</td>
<td>14 (26)</td>
</tr>
<tr>
<td>Retransplantation, n (%)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Deceased donor, n (%)</td>
<td>22 (42)</td>
</tr>
<tr>
<td>Time from transplantation until conception, years</td>
<td>4.4 ± 3.0 (0.1 - 11.9)</td>
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<tr>
<td>Up to 1 year</td>
<td>7 (13)</td>
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<tr>
<td>More than 1 year</td>
<td>46 (87)</td>
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<tr>
<td>Initial immunosuppression, n (%)</td>
<td></td>
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<tr>
<td>CSA/PRED/AZA</td>
<td>9 (17)</td>
</tr>
<tr>
<td>TAC/PRED/AZA</td>
<td>39 (74)</td>
</tr>
<tr>
<td>TAC/PRED</td>
<td>1 (2)</td>
</tr>
<tr>
<td>TAC/PRED/MPA</td>
<td>4 (8)</td>
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<tr>
<td>Immunosuppression at conception, n (%)</td>
<td></td>
</tr>
<tr>
<td>CSA/PRED/AZA</td>
<td>9 (17)</td>
</tr>
<tr>
<td>TAC/PRED/AZA</td>
<td>40 (75)</td>
</tr>
<tr>
<td>TAC/PRED</td>
<td>1 (2)</td>
</tr>
<tr>
<td>TAC/PRED/MPA</td>
<td>3 (6)</td>
</tr>
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</table>
Successfully delivery occurred in 41 (77%) of the pregnancies. Regarding the gestational age, there were 25 (61%) infants born full-term, 9 (22%) infants preterm and 7 (17%) infants born extremely pre-term (< 32 weeks). Forty-nine percent of the infants were delivered by cesarean section. In 41% of the cases, it was necessary to induce labor by maternal medical conditions. There were two cases of perinatal death, corresponding to 3.7% of all pregnancies.

MATERNAL COMPLICATIONS AMONG KIDNEY TRANSPLANT RECIPIENTS

Urinary tract infection was the main maternal complication, and occurred in 23% of the cases. There was one case of gestational diabetes. Among previously normotensive women, 22 pregnancies reached 20 weeks of gestational age. From them, newly diagnosed hypertension occurred in 7 (16%) cases, de novo proteinuria in 20 (45%) cases, and preeclampsia in 5 (11%) cases.

During pregnancy and up to 12 months of follow-up, the incidence of acute rejection confirmed by biopsy was 6%. There was one case of allograft loss, due to immunological atrophy/fibrosis.

There was a significant increase of mean serum creatinine from baseline to the third trimester of pregnancy, and this negative effect was maintained at follow-up, as demonstrated in Table 2 (1.19 ± 0.07 mg/dL at baseline, vs. 1.47 ± 0.15 mg/dL at 3rd trimester, vs. 1.59 ± 0.20 mg/dL at follow-up, p < 0.001). There was a correspondent decline in estimated glomerular filtration rate (eGFR). It was also true for proteinuria (0.08 ± 0.2 g/L at baseline, vs. 0.40 ± 0.08 g/L at 3rd trimester, vs. 0.28 ± 0.06 g/L at follow-up, p < 0.001).

**DISCUSSION**

This study presents a descriptive analysis of a large number of pregnancies occurring in relatively stable kidney transplant patients, and points to potentially serious risks of maternal complications.

At first, although pregnancy has occurred in a non-late age and mostly after the first year post transplantation, as referenced in the literature, the number of miscarriages was higher compared to the Brazilian general population (14%) and also higher in comparison to the incidence of clinically recognizable miscarriage in worldwide general population studies (24% versus 12 to 15%).

Among kidney transplant recipients, studies report that approximately 35% of pregnancies do not progress beyond the 1st trimester due to spontaneous or therapeutic abortion, and that overall success rate is > 90% after the 1st trimester. It is possible that the lower use rates of mycophenolate in our population (only four in 53 pregnancies), known to be associated with increased risk of spontaneous abortion, have influenced the results observed.

With regard to delivery outcome, vaginal delivery is recommended for most transplant recipient in the current guidelines. In our sample, however, as well as in other published studies rates of induction and cesarean section were significantly higher. Oliveira et al., analysing an earlier cohort from the same centre, reported that cesarean section was performed in 61.5% of patients, and the main indication was maternal hypertension and fetal distress syndromes. Unfortunately, in this study we did not evaluate the motive leading to cesarean section. Actually,
The impact of this sustained worsening in renal function over graft survival is a matter for future investigations.

Limitations of this study were its retrospective nature, and the short follow-up time after delivery. It is possible that the number of miscarriages could be underrepresented, since it is a retrospective analysis. In addition, due to bias of information and underreport in the medical charts, it was not possible to collect information about birth defects and newborn outcomes. However, the homogeneity of transplant and obstetrical care provided useful information regarding maternal complications and outcomes.

CONCLUSION

In a single center cohort of stable transplant patients, pregnancy was associated with high rates of maternal complications and miscarriages. The sustained increase of creatinine suggests an increased risk of graft loss in long term. Pregnancy after kidney transplantation should still be considered as a high-risk gestation, and should be approached in a multidisciplinary way. This study demonstrates the need for further analysis regarding the issue of pregnancy and renal transplant.

REFERENCES


