Pregnancy after kidney transplantation: high rates of maternal complications

Gestação após o transplante renal: alto índice de complicações maternas

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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 ± 5years. 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. A imunossupressão preconcepção era composta de tacrolimo, azatioprina e prednisona em 74% dos casos. Houve 15% de aborto no 1º trimestre e 8% no segundo trimestre. Em 41% dos casos, foi necessário induzir o parto. De todos os nascimentos, 22% foram prematuros e 17% muito prematuros. Houve 5% de natimortos e 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.

Introduction

Achieving maternity can still be a challenge for women with chronic kidney disease (CKD). As renal disease progresses, sexual interest and fertility decline.[1] 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.[2] 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.[3]

Data from a recent study, from the United Kingdom national cohort,[4] 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 ($> 10^5$ 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.[5]

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 1 Demography characteristics of the studied population

Variable	n = 53
Mean age at transplantation, years	23 ± 6 (12 - 33)
< 20 years	6 (11)
20 - 34 years	41 (77)
≥ 35 years	6 (11)
Mean age at conception, years	28 ± 5 (17 - 40)
< 20 years	6 (11)
20 - 34 years	41 (77)
≥ 35 years	6 (11)
Ethnicy, n (%)	
Melanodermic	27 (51)
Non-melanodermic	26 (49)
Formal educational level, n (%)	
Iliteracy	1 (2)
Elementary	5 (9)
Secondary	36 (68)
Tertiary	4 (8)
Non available	7 (13)
Cause of end-stage renal disease, n (%)	
Diabetes Mellitus	2 (4)
Glomerulopathy	18 (34)
Unknown	30 (57)
Chronic interstitial nephritis	2 (4)
Oligomeganefronia	1 (2)
Previous treatment, n (%)	
Hemodialysis	50 (94)
Peritoneal	2 (4)
None	1 (2)
Time on dialysis, months	28 ± 26 (0 - 144)
Up to 36 months	39 (74)
More than 36 months	14 (26)
Retransplantation, n (%)	2 (4)
Deceased donor, n (%)	22 (42)
Time from transplantation until conception, years	4.4 ± 3.0(0.1 - 11.9)
Up to 1 year	7 (13)
More than 1 year	46 (87)
Initial immunosuppression, n (%)	
CSA/PRED/AZA	9 (17)
TAC/PRED/AZA	39 (74)
TAC/PRED	1 (2)
TAC/PRED/MPA	4 (8)
Immunosuppression at conception, n (%)	
CSA/PRED/AZA	9 (17)
TAC/PRED/AZA	40 (75)
TAC/PRED	1 (2)
TAC/PRED/MPA	3 (6)

Continuation Table 1.

Preexisting hypertension, n (%)	20 (38)
Baseline proteinuria > 0.5 g/L, n (%)	4 (8)
Multiple pregnancies, n (%)	2 (4)

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[6] (14%) and also higher in comparison to the incidence of clinically recognizable miscarriage in worldwide general population studies (24% *versus* 12 to 15%).[7]

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.[8] 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.[9] In our sample, however, as well as in other published studies[10-12] rates of induction and cesarean section were significantly higher. Oliveira *et al*.,[13] analysing an earlier cohort from the same centre, reported that caesarean 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 caesarean section. Actually,

Table 2 Evolution of renal function and proteinuria among pregnant woman, at baseline, during pregnancy and in follow-up visit

Variable	Baseline	1 Trimester	2 Trimester	3 Trimester	Follow-up	*p*
Serum Creatinine, mg/dL	1.19 ± 0.07	1.08 ± 0.07	1.17 ± 0.10	1.47 ± 0.15	1.59 ± 0.20	< 0.001
Estimated GFR, mL/min/1.73m^2	72.23 ± 26.77	81.10 ± 27.01	80.98 ± 34.66	60.75 ± 23.42	62.04 ± 25.90	< 0.001
Proteinuria, g/L	0.08 ± 0.2	0.12 ± 0.03	0.18 ± 0.05	0.40 ± 0.08	0.28 ± 0.06	< 0.001

GFR: Glomerular filtration rate, estimated by CKD-EPI equation.

Brazilian cesarean rates in the general population are higher than in many other countries in the world, and can reach 61% of all births, according to national data. Many reasons, including socioeconomic factors, may explain these high rates.[14]

Premature birth is a major problem among kidney transplant recipients, occurring in 40 - 60% of cases. That is twice to three times higher than in general population, in which incidence varies from 5-15 %.[8] The results in the present study are in agreement with the literature. The majority of babies were intentionally premature delivered, usually due to maternal medical conditions like preeclampsia.

Infection and particularly urinary tract infection is the most common complication after kidney transplantation,[15] with a reported incidence of 19-40%.[8] We observed a rate of 23% of urinary tract infection, even under continuous antimicrobial prophylaxis with cotrimoxazole. Physiological changes in the urinary tract occurring during pregnancy cause dilatation of renal collecting system and the increase of bacterial growth due to the altered composition of the urine.

Regarding high blood pressure, it is well known that it is prevalent among patients with chronic kidney diseases, persists after kidney transplantation, and worsens in patients on calcineurin inhibitors therapy.[9] Regarding proteinuria, it is also known that it can be present after transplant due to a myriad of cases, like recurrent or de novo glomerulopathies, transplant glomerulopathy, and overflow.[16] Because of these confounding factors, diagnosis of preeclampsia may be hidden in transplanted women. In our sample, using the strict definitions adopted, preeclampsia was diagnosed in 11% of cases.

One of the most important aspects in our study was the significant and sustained rise in creatinine and decline in eGFR during pregnancy and at follow-up. In previous studies, pregnancy did not appear to impair renal function in stable transplant patients.[17] The demographic characteristics of our population may be different. It points out that a large number of women (17 out of 36) had more than one pregnancy during the respective period of study. Furthermore, the immunosuppression regimen, the duration of the follow-up period, and the number of visits during pregnancy were different in several studies presented, contributing to the different results in our population. 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 transplanted women, 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

1. Groothoff J. Pregnancy during dialysis: still a challenge to get there, but worth the effort. Nephrol Dial Transplant 2015;30:1053-5. DOI: http://dx.doi.org/10.1093/ndt/gfv124
2. McKay DB, Josephson MA. Pregnancy in recipients of solid organs-effects on mother and child. N Engl J Med 2006;354:1281-93. DOI: http://dx.doi.org/10.1056/NEJMra050431
3. Davison JM, Bailey DJ. Pregnancy following renal transplantation. J Obstet Gynaecol Res 2003;29:227-33. DOI: http://dx.doi.org/10.1046/j.1341-8076.2003.00106.x
4. Bramham K, Nelson-Piercy C, Gao H, Pierce M, Bush N, Spark P, et al. Pregnancy in renal transplant recipients: a UK national cohort study. Clin J Am Soc Nephrol 2013;8:290-8. DOI: http://dx.doi.org/10.2215/CJN.06170612
5. American Congress of Obstetricians and Gynecologists. Hypertension in Pregnancy [Internet] [cited 2016 Feb 10]. Available from: http://www.acog.org/Resources_And_Publications/Task_Force_and_Work_Group_Reports/Hypertension_in_Pregnancy
6. Cecatti JG, Guerra GVQL, Sousa MH, Menezes GMS. Aborto no Brasil: um enfoque demográfico. Rev Bras Ginecol Obstet 2010;32:105-11. DOI: http://dx.doi.org/10.1590/S0100-72032010000300002
7. Regan L, Rai R. Epidemiology and the medical causes of miscarriage. Baillières Best Pract Res Clin Obstet Gynaecol 2000;14:839-54. DOI: http://dx.doi.org/10.1053/beog.2000.0123
8. Stratta P, Canavese C, Giacchino F, Mesiano P, Quaglia M, Rossetti M. Pregnancy in kidney transplantation: satisfactory outcomes and harsh realities. J Nephrol 2003;16:792-806.
9. Díaz JM, Canal C, Giménez I, Guirado L, Facundo C, Solà R, et al. Pregnancy in recipients of kidney transplantation: effects on mother and child. Nefrologia 2008;28:174-7.

10. Deshpande NA, James NT, Kucirka LM, Boyarsky BJ, Garonzik-Wang JM, Montgomery RA, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. Am J Transplant 2011;11:2388-404. DOI: http://dx.doi.org/10.1111/j.1600-6143.2011.03656.x
11. Levidiotis V, Chang S, McDonald S. Pregnancy and maternal outcomes among kidney transplant recipients. J Am Soc Nephrol 2009;20:2433-40. DOI: http://dx.doi.org/10.1681/ASN.2008121241
12. Cândido C, Viegas M, Matias P, Birne R, Jorge C, Weigert A, et al. Pregnancy in renal transplanted patients: effects on the mother and the newborn - 29 years of experience in a single centre. Port J Nephrol Hypertens 2015;29:228-35.
13. Oliveira LG, Sass N, Sato JL, Ozaki KS, Medina Pestana JO. Pregnancy after renal transplantation - a five-yr single-center experience. Clin Transplant 2007;21:301-4. DOI: http://dx.doi.org/10.1111/j.1399-0012.2006.00627.x
14. Brasil. Ministério da Saúde. DATASUS. TabNet Win32 3.0: F.8 Proporção de partos cesáreos. [Internet] [cited 2016 Feb 21]. Available from: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?idb2010/f08.def
15. Cristelli MP, Tedesco-Silva H, Medina-Pestana JO, Franco MF. Safety profile comparing azathioprine and mycophenolate in kidney transplant recipients receiving tacrolimus and corticosteroids. Transpl Infect Dis 2013;15:369-78. DOI: http://dx.doi.org/10.1111/tid.12095
16. Roberts M, Lindheimer MD, Davison JM. Altered glomerular permselectivity to neutral dextrans and heteroporous membrane modeling in human pregnancy. Am J Physiol 1996;270:F338-43. PMID: 8779896
17. Armenti VT, Radomski JS, Moritz MJ, Philips LZ, McGrory CH, Coscia LA. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2000:123-34. PMID: 11512306