La grossesse chez les greffées rénales : Quelles sont les conditions optimales pour une meilleure issue des grossesses ?

Pregnancy in kidney transplanted women: What are the optimal conditions for a better pregnancy outcome?

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RÉSUMÉ

Prérequis: La maternité a longtemps été déconseillée chez la femme transplantée rénale par peur des effets délétères sur le greffon et les risques encourus par le fœtus.

But : Répondre de façon factuelle aux questions relatives à la grossesse chez les femmes transplantées rénales:
1. quels sont les paramètres néphrologiques et obstétricaux qui peuvent influencer le déroulement de la grossesse?
2. Quel est l'impact de la grossesse sur le greffon?
3. Quelles sont les conditions optimales pour planifier une grossesse chez les femmes transplantées rénales?

Méthodes: Une recherche a été effectuée en utilisant les mots clés "grossesse", "transplantation rénale", "la survie du greffon rénal" sur PubMed au cours de la période allant de Janvier 1994 à Décembre 2011.

Résultats: Le rétablissement de la fonction rénale chez les patientes transplantées rénales est suivi du rétablissement des fonctions endocriniennes. La connaissance de la néphropathie initiale permet d'évaluer le risque de récidive après la transplantation, pouvant toucher le greffon pendant la grossesse. Les néphropathies glomérulaires chroniques sont les plus fréquentes de 32 à 76,1 %. L'ancienneté en hémodialyse (supérieure à 2 ans) est corrélée à un risque d'accouchement prématuré et de retard de croissance. Un délai entre transplantation rénale et conception de 1 an semble raisonnable pour stabiliser la fonction rénale et réduire les doses des immunosuppresseurs. Le nombre de grossesses non planifiées reste élevé (50%). La fréquence des grossesses après la transplantation rénale varie entre 3 et 21,2 %. La survie du greffon chez les patientes ayant mené une grossesse est équivalente à celle des patientes qui n'ont pas été enceintes.

Conclusion : La grossesse chez les patientes transplantées du rein est une grossesse à haut risque, mais elle ne semble pas altérer la fonction du greffon sous réserve de certaines conditions.

Mots-clés
Greffe rénale, grossesse, pré-éclampsie, prématurité.

SUMMARY

Background: Motherhood has long been not recommended for kidney transplanted women for fear of adverse effects on the graft and the risks to the fetus.

Aims: This article aimed to provide evidence based answer to the following questions regarding pregnancy in kidney transplanted women:
1. what are the nephrologic and obstetrical parameters that can influence the pregnancy outcome?
2. What is the impact of pregnancy on graft?
3. What are the optimal conditions for pregnancy planning in kidney transplanted women?

Methods: A literature search was conducted using as key words "pregnancy", "renal transplant", "renal graft survival" in the PubMed database over the period from January 1994 to December 2011.

Results: Recovery of renal function in kidney transplanted patients is followed by restoration of endocrine function. Knowledge of the initial nephropathy assesses the risk of recurrence after transplantation, which may affect the graft. Chronic glomerular nephropathies are the most frequent from 32 to 76.1%. Duration of hemodialysis (over 2 years) is associated with a risk of preterm delivery and growth retardation. A period of 1 year between renal transplantation and conception seems reasonable to stabilize renal function and reduce the doses of immunosuppressants. The number of unintended pregnancies remains high (50%). The incidence of pregnancy after renal transplantation varies between 3 and 21.2%. Graft survival in patients who carried a pregnancy is equivalent to that of patients who were not pregnant.

Conclusions: Pregnancy in kidney transplanted patients is a high-risk pregnancy, but it does not seem to affect graft function through certain conditions.

Key-words
Renal graft, pregnancy, pre-eclampsia, prematurity.

Kidney transplantation is undoubtedly a turning point in the lives of patients suffering from renal failure. In addition to improving the quality of life and prognosis, it is a legitimate hope for all those who want to conceive. Recovery of renal function is followed by the restoration of endocrine function allowing pregnancy. Motherhood has long been not recommended for kidney transplanted women by fear of deleterious effects on graft. Nowadays, under certain conditions, pregnancy in kidney graft is possible.

This article aimed to provide evidence based answer to the following questions regarding pregnancy in kidney transplanted women:

1. what are the nephrologic and obstetrical parameters that can influence the pregnancy outcome?
2. What is the impact of pregnancy on graft?
3. What are the optimal conditions for pregnancy planning in kidney transplanted women?

METHODS

A literature search was conducted using as key words “pregnancy”, “renal transplant”, “renal graft survival” in the PubMed database over the period from January 1994 to December 2011, by taking as language of publication French and English. We retained the original articles, reviews and reports of national transplantation registers. Editorials and abstracts were excluded. All selected articles were analyzed qualitatively.

By introducing the key words “pregnancy”, “renal transplant”, “renal graft survival” on the Pubmed database, we obtained 244 publications. Only 31 articles match the eligibility criteria mentioned above and were used in this work.

RESULTS

Nephrological parameters

Chronic glomerular nephropathies (CGN) are recognized in many studies as the most common cause of kidney failure at the origin of the development of chronic hemodialysis in transplanted kidney patients and in whom pregnancy occurred after transplantation. CGN rate was 39.6% in a study by Gill et al. [1], 32% in a study by Areia et al. [2], 52% in a study by Kim et al. [3], 76.1% in a study by Kurata et al. [4], 58.8% in a study by Yildrim et al. [5], 41% in a study by Ehrich et al. [6] and 43.6% in study Rahamimov et al. [7]. The identification of the initial nephropathy is necessary to assess risk of recurrence after transplantation, risk for the graft during pregnancy, or a risk of recurrence in the offspring [8,9]. It does not seem to be useful for predicting the occurrence of pregnancy in a patient who received a kidney transplant [2,3]. A study conducted in 2009 [1] concluded that patients who had renal failure as a result of diabetes were less likely to conceive than those whose initial nephropathy was CGN.

In most studies [5-8], the duration of the dialysis before transplantation has not been evaluated. Long standing hemodialysis correlates with accelerated atherogenesis and is associated with a risk of preterm delivery, growth retardation and fetal distress. Kurata found that duration of hemodialysis to transplantation superior to 2 years was related to the occurrence of preterm delivery less than 35 weeks. But this parameter was not found as significant factor of preterm delivery [4]. Gill found no significant association between length of dialysis and the probability to conceive. The decrease in the rate of pregnancy among kidney transplant was explained by the wider use of immunosuppressant drugs including cyclosporine in the treatment of CGN prior to renal transplantation [1].

Kidney transplantation is the best treatment for end-stage renal disease. Patients who benefited from a kidney transplant have a longer life, better quality of life and consume fewer health care resources than patients on chronic dialysis [10-12]. The mean age at transplantation ranged from 23.6 years to 33.4 years, according to studies [1, 3, 7, 8]. The data analysis of the study by Kim and al concluded that younger age at transplantation was a significant predictor for a positive result in the birth of a living child [3].

Parameters related to pregnancy

Planning, a crucial step, as well as monitoring the pregnancy are the result of close collaboration between the obstetrician and the nephrologist. In general, women at the age of procreation are informed of their possibility of conception and recommended for adequate contraception. If pregnancy is desired, the patient is assessed for renal function with stabilization of associated diseases: high blood pressure equilibration, equilibration of diabetes, treatment of infection. The number of unintended pregnancies remains high (about 50%) in several studies [5, 13-15]. A retrospective study by Keitel (2004) about 44 pregnancies occurred in 41 patients, concluded that pregnancy did not affect the survival of the patient and long-term graft while only 5 pregnancies were conducted in the absence of risk factor [13].

Several studies have recommended waiting a period of 2 years after transplantation before allowing patients to conceive [5,7,15,15-19]. In a recent study, Gorgulu reported that a longer period between renal transplantation and conception is related with a lower rate of premature babies and children born with low birth weight [16]. This attitude was considered too conservative by a study conducted in 2009 by Gill about 530 pregnancies in 483 renal transplanted patients [1]. His findings support current recommendations regarding the timing of pregnancy after transplantation, including the suggestion that a 2-year waiting period between transplantation and attempts at conception may be overly conservative.

Kim have recently (2008) concluded that a delay Kidney Transplantation-Conception less than or equal to 1 year was not associated with a higher risk of complications compared with a group of patients whose waiting time before pregnancy was more than one year [3]. Although an optimal interval between transplantation and the design has not yet been established, the National Transplantation Pregnancy Registry (NTPR) and the American Society of Transplantation (AST) suggested waiting 1 year after transplantation, this delay is reasonable to stabilize the renal function and reduce the doses of immunosuppressive drugs [20, 21].

The incidence of pregnancy after renal transplantation has varied from one study to another. Ghanem reported a rate of 21.2% (Of 193 patients of childbearing age, 41 had at least one pregnancy) [19]. In the study by Kim, only 10% of patients of childbearing age have a pregnancy [3] and the rate was even lower in the study by Gill less than 3% (483 of 1619) [1]. The live birth rates ranged from 55.4% to 90% [1,3,5,14,18,19,22].

Complications during pregnancy

The incidence of hypertension among patients transplanted kidney varies from 60% to 80% [23]. Several factors are involved in the onset of hypertension after renal transplantation: immunosuppressive therapy including corticosteroids and cyclosporine, graft function, the nature of the donor, obesity, alcohol, smoking, presence of a native kidney (increased production of renin) [23,24]. The diagnosis of preeclampsia can be difficult due to the frequency of hypertension and proteinuria in kidney transplanted patients [25-27]. Yidirim et al. reported in their study that 15% of patients are worsening hypertension without preeclampsia [5]. Elevation of blood pressure and taking antihypertensive were significantly associated with risk of premature delivery and low birth weight [22].

During pregnancy, the ureter compressed by the gravid uterus expands [27]. The risk of acute pyelonephritis is particularly increased especially in immunodepressed patients. Cruz Lemini [14] reported a frequency of 45.3% urinary tract infections in agreement with that reported by Davison and Milne 40% [9]. The gestational diabetes is a complication even more common with the use of steroids but also of cyclosporine and tacrolimus, gestational diabetes was found in a frequency of 5% to 29.3% [5,14,19].

Delivery and newborn

In most studies, the term at delivery ranged from 35.6 ± 0.3 to 38 weeks of gestation [3,5,17]. Premature rupture of membranes (PROM) was noted in 11% to 17%. It has often been responsible for caesarean section [14, 22]. The preterm birth rate was high in this population estimated at 45-60% of cases [25]. In literature, the rate of premature births found by Yildirim et al is one of the lowest observed (31.25%) (5). This is related to compliance with international recommendations and the fact that patients had a serum creatinine less than 125 µmol / l before conception.

The cesarean rate ranges from 40% to 100%, is probably not justified solely by obstetric indications [2,14,18,19,22]. Low birth weight was reported by Sibanda and Ducarme respectively 54% and 40% [18,19]. Intrauterine growth retardation is associated with the use of cyclosporine and prematurity [25].

Long-term follow-up

Most studies have shown that graft survival in patients who had a pregnancy was equivalent to that of patients who were not pregnant [7,28,29]. The NTPR (National Transplantation Pregnancy Registry) found that graft loss in patients who had a pregnancy fluctuated between 4% and 14% within two years after delivery. These rates are similar to those observed in renal transplant who were not pregnant [30]. Data on children from these special pregnancies are reassuring. Nulman compared 39 children exposed in utero to cyclosporine in kidney transplanted patients with a control group of 38 children. No significant differences were found in neurocognitive and behavioral development [31].

CONCLUSION

Renal transplantation allows patients suffering from end-stage renal disease improving quality of life and represents a legitimate hope for all those who want to conceive. Pregnancy in kidney transplanted patients is a high risk pregnancy because of the higher incidence of low birth weight, prematurity and intrauterine growth retardation. A favorable outcome of pregnancy and the preservation of renal graft is possible through: planning pregnancy (stable renal function and hypertension balanced), monitoring conducted in coordination with the gynecologist and the nephrologist and childbirth in a maternity of 3rd level.

For a better understanding of the particularities of pregnancy in kidney transplanted patients in Tunisia, the establishment of a national registry collecting information from all centers of kidney transplant, all services of Gynecology and Obstetrics and free practice physicians is necessary.

References

1. Gill JS, Zalunardo N, Rose C, Tonelli M. The pregnancy rate and live birth rate in kidney transplant recipients. Am J transplant 2009;9:1541-9.
2. Areia A, Galvao A, Pais MS, Freitas L, Moura P. Outcome of pregnancy in renal allograft recipients. Arch Gynecol Obstet 2009;279:273-7.
3. Kim HW, Seok HJ, Kim TH, Han DJ, Yang WS, Park SK. The experience of pregnancy after renal transplantation: Pregnancies even within postoperative 1 year may be tolerable. Transplantation 2008;85:1412-9.
4. Kurata A, Matsuda Y, Tanabe K, Toma H, Ohta H. Risk factors of preterm delivery at less than 35 weeks in patients with renal transplant. Eur J Obstet Gynecol Reprod Biol 2006;128:64-8.
5. Yildirim Y, Uslu A. Pregnancy in patients with previous successful renal transplantation. Int J Gynaecol Obstet 2005;90:198-202.
6. Ehrich JH, Loirat C, Davison JM et al. Repeated successful pregnancies after kidney transplantation in 102 women (reported by the EDTA Registry). Nephrol Dial Transplant 1996;11:1314-7.
7. Rahaminov R, BenHaroush A, Wittenberg C et al. Pregnancy in renal transplant recipients: Long Term effect on patient and graft survival. A single-center experience. Transplantation 2006;81:660-4.
8. Kashanizadeh N, Nemati E, Sharifi-Bonab M et al. Impact of pregnancy on the outcome of kidney transplantation. Transplant Proc 2007;39:1136-8.
9. Davison JM, Milne JE. Pregnancy and renal transplantation. Br J Urol 1997;80:29-32.
10. Wolfe RA, Ashby VB, Milford EL et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting for transplantation and recipients of a first cadaveric transplant. N Engl J Med 1999;341:1725-30.
11. Laupacis A, Keown P, Pus N et al. A study of the quality of life and cost-utility of renal transplantation. Kidney Int 1996;50:235-42.
12. Winkelmayer WC, Weinstein MC, Mittleman MA, Glynn RJ, Pliskin JS. Health economic evaluations: The special case of end-stage renal disease treatment. Med Decis Making 2002;22:417-30.
13. Keitel E, Bruno RM, Duarte M et al. Pregnancy outcome after renal transplantation. Transplant Proc 2004;36:870-1.
14. Cruz Lemini MC, Ochoa FI, Villanueva Gonzalez MA. Perinatal outcome following renal transplantation. Int J Gynaecol Obstet 2007;96:76-9.
15. Basaran O, Emiroglu R, Seçme S, Moray G, Haberal M. Pregnancy and renal transplantation. Transplant Proc 2004;36:122-4.

16. Gorgulu N, Yelken B, Caliskan Y, Turkmen A, Sever MS. Does pregnancy increase graft loss in female renal allograft recipients? Clin Exp Nephrol 2010;14:244-7.
17. Ben Aissia N, Battar S, Gara MF. Les particularités de la grossesse et de l'accouchement après greffe rénale. Tunis Med 2003;81:55-8.
18. Ducarme G, Ceccaldi PF, Toupance O, Graesslin O, Rieu P, Gabriel R. Grossesse après transplantation rénale. Suivi obstétrical et retentissement sur le greffon rénal. Gynecol Obstet Fertil 2006;34:209-13.
19. Ghanem ME, El-Baghdadi LA, Badawy AM, Bakr MA, Sobe MA, Ghoneim MA. Pregnancy outcome after renal allograft transplantation: 15 years experience. Eur J Obstet Gynecol Reprod Biol 2005;121:178-81.
20. Armenti VT, Daller JA, Constantinescu S et al. Report from the National Transplantation Pregnancy Registry: outcomes of pregnancy after transplantation. Clin Transplant 2006:57-70.
21. McKay DB, Josephson MA, Armenti VT et al. Reproduction and transplantation: Report on the AST Consensus Conference on Reproductive Issues and Transplantation. Am J Transplant 2005;5:1592-9.
22. Sibanda N, Briggs D, Davison JM, Johnson RJ, Rudge CJ. Pregnancy after organ transplantation: a report from the U.K.Transplant Pregnancy Registry. Transplantation 2007;83:1301-7.
23. First MR, Neylan JF, Rocher LL, Tejani A. Hypertension after renal transplantation. J Am Soc Nephrol 1994;4:30-6.
24. Haas M, Mayer G. Cyclosporine Associated hypertension: patho-mechanisms and clinical consequences. Nephrol Dial Transplant 1996;12:395-8.
25. Davison JM, Bailey DJ. Pregnancy following renal transplantation. J Obstet Gynaecol Res 2003;29:227-33.
26. Aivazoglou L, Sass N, Silva Jr HT, Sato JL, Medina-Pestana JO, De Oliveira LG. Pregnancy after renal transplantation: an evaluation of the graft function. Eur J Obstet Gynecol Reprod Biol 2011;155:129-31.
27. Fuchs KM, Wu D, Ebcioglu Z. Pregnancy in renal transplant recipients. Semin Perinatol 2007;31:339-47.
28. Sturgiss SN, Davison JM. Effect of pregnancy on the long-term function of renal allografts: an update. Am J Kidney Dis 1995;26:54-6.
29. First MR, Combs CA, Weiskittel P, Miodovnik M. Lack of effect of pregnancy on renal allograft survival or function. Transplantation 1995;59:472-6.
30. 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 Transplant 2000:123-34.
31. Nulman I, Sgro M, Barrera M, Chitayat D, Cairney J, Koren G. Long-term neurodevelopment of children exposed in utero to ciclosporin after maternal renal transplant. Pediatr Drugs 2010;12:113-22.