

*Full Length Research Paper*

# Renal Transplantation and Pregnancy: Managing Risks and Complications

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Received 20 September, 2024; Accepted 14 January, 2025

Fertility is considerably affected in chronic renal insufficiency and periodic hemodialysis, and it is improved by renal transplantation. Transplanted patients recover from their renal failure state, and pregnancy occurred in 2% renal graft recipients who were fit to procreate. The aim of this study was to bring back the cases of pregnancies carried out in our renal patients who had transplantation surgery and to specify the possible complications of the foetus before and after the childbirth. It is a retrospective study with records of 20 years period (1986 to 2006) of 10 pregnancies which occurred in 7 renal transplant recipients in our Charles Nicole hospital department. Mean patient age was 33.8 years (29 to 43 years). Mean time between transplantation and the onset of pregnancy was 6.5 years (1 to 18 years). Before pregnancy, hypertension was observed in 1 case and proteinuria in other case. All our patients had creatininemia <1.50 mg/dl. Immunosuppressive treatment associated steroids and azathioprin in 3 cases, steroids and ciclosporin A in 2 cases and steroids, ciclosporin A and azathioprin in 2 cases. One patient developed diabetes. Maternal complications were rare, essentially hypertension in 2 cases, proteinuria in 1 case, ascension of creatininemia in 2 cases and hepatic cholestase in 2 cases. Prematurity was observed in 2 cases; it was related to premature rupture of membranous in 1 case and uterine contractions in cesarean patient in other case. The mean neonatal weight was 2950 g (2100 to 3500 g) with 4 small gestational age (< 2800 g). It was noted in 1 case of newborn, down's syndrome in a pregnant women who was 37 years. After a mean follow up of 7.4 years follow-up, mean cretininemia was 1.80 mg /dl (0.74-5.53 mg /dl). One patient showed chronic rejection. Immunosuppressive treatment seemed without adverse effects on fetus. The only case of chromosome abnormality appeared in a pregnant women who was more than 35 years old. The course of pregnancy after renal transplantation is generally uncomplicated without increased risk of graft loses. However, a normal arterial pressure, a stable renal function and absence of proteinuria were requested before allowing a pregnancy.

**Key words:** Renal transplantation, pregnancy.

## INTRODUCTION

Women with end-stage chronic renal failure have low fertility and high-risk pregnancies (Fuchs et al., 2007).

Kidney transplantation in most cases restores fertility for these women (Audra and Laville 1996; Ville et al.,

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1992) . 14 000 births in the whole world were reported in organ transplant recipients (Mc Kay and Josephson 2006). The first pregnancy after organ transplantation was recorded in 1963 in a woman who had received a kidney allograft (Audra and et Laville 1996) and since it was successful pregnancies were reported in 2% of kidney transplant recipients of childbearing age (First et al., 1995; Davison 2006). However, pregnancy in kidney transplant recipients is not without risks (Fuchs et al., 2007; Ben Youssef et al., 2006). The course of the pregnancy is favorable by respecting the recommendations such as the European recommendations of good practices IV (Fuchs et al., 2007; O' Bas aran et al., 2004). The objective of our study, was to study the course of pregnancy after kidney transplantation and to assess the impact of the pregnancy on the fetus and on the kidney graft.

## METHODOLOGY

### Patients

This is the retrospective study of the medical histories of 312 kidney transplant recipients whose operations were performed between 1986 and 2006 in our hospital. Kidney transplant recipients received likely a living related graft in 241 cases, a non related graft in 17 cases and a cadaveric graft in 54 cases. Among the 107 kidney transplantation in females, 10 spontaneous pregnancies occurred in 7 kidney transplant recipients. We had contra-indicated pregnancy during the first 2 years after kidney transplantation.

### Experimental

Patients were reviewed in terms of the reason for kidney failure, type of dialysis (hemodialysis or peritoneal dialysis), length of pretransplant dialysis and age at kidney transplantation. For donors, these demographics included age, sex, blood group, type of donor (deceased or living), and relationship to the recipient. For each patient, transplantation-pregnancy interval, age at diagnosis of pregnancy, immunosuppressive regimen, and function of the kidney at the time of diagnosis of pregnancy circumstances of discovery of the pregnancy and its complications were reviewed. Arterial pressure and labour values were all evaluated. Graft function and mortality rate were also reviewed. The infants' general health and follow-up were examined closely. The mode of delivery (natural childbirth or cesarean section), the baby's weight, length, head circumference, Apgar score and labor values were all evaluated. Low-birth-weight is defined by weight between 1500 and 2500 g and very low-birth-weight by weight between 1000 to 1500 g at birth. Premature babies are delivered between gestational weeks 29 and 37. We also inquired about growth, laboratory tests, and the last measured height and weight.

## RESULTS

The mean age at kidney transplantation was 28.5 years (25 to 35 years). Causes of the end stage renal stage were interstitial in 3 cases (nephronoptis in 1 case), glomerular in 2 cases (IgA nephropathy in 1 case and

membranous nephropathy in 1 case) and unknown in 2 cases. Kidney transplant recipients received a living related graft in 5 cases and a cadaveric graft in 2 cases. Immunosuppressive regimen associated steroids and azathioprine with or without ciclosporine. A patient presented a microscopic hematuria and a graft dysfunction explained by the recurrence of Ig A nephropathy on the kidney graft. Hypertension was observed in 2 cases, proteinuria in 2 cases under 1 g/24 h, anemia in 1 case and post transplantation diabetes in 1 case. The mean serum creatininemia before pregnancy was at 1.03 mg /dl (0.81- 1.47 mg /dl). No case of acute rejection of the graft was observed before diagnosis of pregnancy. Patients had regular menstrual cycles and were not under contraception. (Table 1) Circumstances of discovery of the pregnancy were delay by the menstruations in all the cases. The mean interval from transplantation to pregnancy was 6.5 years (1 to 18 years) and it was higher than 2 years in 70% of the cases. The mean age at diagnosis of pregnancy was 33.8 years (29 to 43 years). No modification of immunosuppressive regimen was noted during pregnancy.

The mean creatininemia during pregnancy was constant at 1.04 mg /dl (0.77 to 1.88 mg /dl) with the creatininemia higher than 1.5 mg /dl in 2 cases. Pregnancy complications included new-onset proteinuria in 1 case in the third trimester and the onset of hyper-tension without proteinuria in 1 case. The hypertension was associated with proteinuria in 3 cases. Graft dysfunction during pregnancy was observed in 2 cases, hepatic cholestasis in 2 cases and hyperuricemia in 4 cases. No peripartum maternal deaths were reported (Table 2).

Fetal complications were premature in 3 cases caused by a premature rupture of the membranes in 1 case, uterine contractions on cicatricial uterus in 1 case and preeclampsia in the third case. Mean weight at birth was 2950 g (2100 to 3500 g) with 4 cases of low-birth-weight. A patient presented an allograft dysfunction caused by an infection of the amniotic liquid. Postpartum was without complications in all the cases. Only one patient was lost to follow-up after the childbirth. Six patients were followed. After a mean follow-up of 7.4 years (2 to 14 years) after childbirth, blood pressure was normal in 3 patients and hypertension was observed in 3 patients. No acute rejection was noted. Renal function remained stable in 9 cases. A puncture biopsy of the graft practiced in the patient having creatininemia at 5.53 mg /dl showed chronic allograft dysfunction and chronic ciclosporine toxicity with tubulointerstitial and vascular lesions.

Concerning the 3 patients who had 2 pregnancies, after a follow-up respectively of 4, 6 and 14 years, hypertension was noted in 2 cases, creatininemia was respectively at 1.12; 1.40 and 1.06 mg /dl and proteinuria was observed in 1 case. One death was observed 8 years after the childbirth secondary to colic cancer. Growth was normal for 9 children. Only one baby had down syndrome whose mother was 36 years old (Table 3).

**Table 1.** Clinical exam and biology before pregnancy.

NI	Age at KT (year)	Donor age (years)	Ttt IS	BP cmHg	Treatment	Creat (mg /dl)	Gly (mmol/l)	Uric acid (µmol/l)	Hb (g/dl)	Hepatic biology	24 h- Proteinuria (g)
NIC/PBR: nephronophthisis	28	Mother (47)	CS- AZT	11/7	0	0.98	5.8	264	13.2	NI	0
				12/8	0	0.94	5	317	12.6	NI	0
NIC/RVU	28	Mother (57)	CS- AZT-CicloA	12/8	0	1.36	4.8	435	9.5	NI	0
NGC/PBR: nephropathy	25	Deceased	CS-AZT	11/6	0	1.47	5.7	393	12.2	NI	0.5
				12/8	metoprolol	1.39	5	378	12.2	NI	0.8
NIC	23	Mother (44)	CS-CicloA	11.5/7	0	0.91	5.2	309	14.2	NI	0
				9/6	0	0.81	5	300	13.5	cytolysis	0
NC/PBR inconclusive	31	deceased	CS-CicloA	13/9	metoprolol	0.84	4.4	205	13.5	NI	0
NGC/PBR:GEM	35	Brother (30)	CS-AZT-CicloA	11/6	0	0.81	5.8 (diabetes)	334	12.6	NI	0
NC	30	Brother (30)	CS-AZT	12/8	0	0.80	5	300	12	NI	0

AZT: azathioprin, BP: blood pressure, Cs : steroids, CicloA: ciclosporine, Creat: creatininemia, Gly: glycemia, Hb: haemoglobin, K T : kidney transplantation, NI: normal, Prot/24h: 24-hours proteinuria.

**Table 2.** Clinical exam and biology during pregnancy.

Interval KT/P (years)	BP cmHg	Treatment	Creat mg /dl	Gly mmol/l	Uric acid µmol/l	Hb g/dl	Hepatic biology	24h- Proteinuria (g)
1	10.5/8	0	0.83	5.5	273	9.8	NI	0
3	11.5/7	0	0.77	5	274	10	NI	0
2	12/8	Acebutolol	1.60	5	532	7.5	NI	0
12	11/6	0	1.88	5.5	525	12	NI	1.5
18	13/9	metoprolol	1.40	5	458	12.2	NI	0.9
7	12/8	0	0.75	5	291	10.8	cholestasis	0
10	12/8	0	0.75	5	300	10.4	cholestasis	0
4	11/8	Acébutolol	0.94	5 (diabetes)	300	8.7	NI	0.8
2	12/8	0	0.76	5.5	501	12	cholestasis	0
6	12/8	0	0.80	5	300	11	NI	0

BP: blood pressure, Creat: creatininemia, Gly: glycemia, Hb: haemoglobin, K T : kidney transplantation, NI: normal, P:pregnancy, Prot/24h: 24-hours proteinuria.

**Table 3.** Complications in fetuses or neonates and kidney recipients mothers.

Follow-up (years)	Fœtus	Mother
14	-	
12	-	HBP
4	Preterm delivery-	Cesarean section
11	-	
5	-	Cesarean section -HBP-prot =0,5g/24h
7	-	
4	Preterm delivery	RAS
8	-	ARF (amniotic infection) – cesarean section HBP-CGD-prot =0,6g/24h death
2	Preterm delivery-	Cesarean section
Lost to follow-up	Down's syndrome	-

ARF: acute renal failure, CGD: chronic graft dysfunction, HBP : High blood pressure.

## DISCUSSION

In this study, 6.5% of childbearing age women experienced pregnancy, an incidence that was lower than what was recently reported (49). Since successful pregnancies were reported in 2% of kidney transplant recipients (First et al., 1995; Davison 2006). All pregnancies occurred after 1 year post transplantation; creatinemia was lower than 150 µmol/l in all cases, normal blood pressure under treatment in 2 cases and a proteinuria under 1 g/24 h in 2 cases.

The maternal complications during the pregnancy were gravidic arterial hypertension in 3 cases, proteinuria in 3 cases, hepatic cholestasis in 2 cases and hyperuricemia in 4 cases. A patient presented an acute renal failure due to amniotic liquid infection. The fetus complications were premature in 3 cases and a fetal hypotrophy in 4 cases. One case of Down's syndrome whose mother was 36 years old is noted. Kidney transplantation improved the fertility in chronic failure patients (Fuchs et al., 2007). Several registers studied the course of these pregnancies (Coscia et al., 2007; Sibanda et al., 2004).

These pregnancies were rare, occurring in 97% of cases after the first year of kidney transplantation (Levidiotis et al., 2009). All our patients carried out a pregnancy test after the first year of renal transplantation. The mean age at the time of these patients were 29±5 years comparable with that of our patients (Levidiotis et al., 2009). Multiple pregnancies are rarer (Nicovani et al., 2009). Pregnancy must be planned since risk factors increase to 75% of the maternal and/or fetal complications (Davison 2006; Davison 1995; Fitoussi et al., 1990 ; Ross 2006).

The risk factors are a short interval between kidney transplantation and pregnancy lower than 2 years, a pre conceptional controlled hypertension, a creatinemia > 1.50 mg/dl and a proteinuria. Immunosuppressive treatment must be adapted (Rizzoni et al., 1992; Armenti

et al., 1995; Armenti et al., 2008; Framarino et al., 2007). Prematurity in these patients are more frequent in our study than in other literatures in general population (30 to 92% versus 12.5%) (Framarino et al., 2007; Armenti et al., 1994; Muirhead et al., 1992; Davison et al., 1976; Blowey and Warady 2007; Rudolph et al., 1979). Prenatal steroid therapy is indicated in some cases to reach fetal pulmonary maturation (Hibbard 2007). In our series, a prematurity was observed in 2 cases. The fetal hypertrophy is more frequent than in the general population (8 to 45 % versus 5%) particularly when creatinemia is > 1.50 mg/dl, there is an hypertension (Davison et al., 1976; Framarino di Malatétaita et al., 1993; Nojima et al., 1996) during treatment by ciclosporine compared to the azathioprine (Haugen et al., 1994; Pickrell et al., 1988; Williams et al., 1988). In our series, the fetal hypertrophy was observed in 4 cases in spite of a creatinemia lower than 1.50 mg /dl in our patients. Opportunist infections are life threatening to the fetus (Hibbard 2007).

The teratogenicity risk of the immunosuppressive drugs is possible with important doses except mycophenolate mofetil taken during the pre-conceptional period responsible for cranio -facial and cardiovascular malformations (Haugen et al., 1994; Pickrell et al., 1988; Williams et al., 1988; Anderka et al., 2009; Dei Malatétaita et al., 2009). It is then recommended to plan a pregnancy if doses of corticoids are lower than 15mg/j, ciclosporine lower than 15 mg/j and azathioprine lower than 2 mg/kg/j (3). It is also recommended to stop the mycophenolate mofetil and to replace it by the azathioprine 2 months before conception. In our series, the only case of chromosomal aberration appeared with the waning of a late pregnancy. We have not noted any case of neonatal mortality which is more important in literature than that in general population (1 to 39% versus 0.68%) (Blowey and Warady, 2007). After birth, the psychomotor development of the children is normal

(Nicovani et al., 2009).

The maternal complications are mainly hypertensive in 38 to 56% aggravated by steroids and ciclosporine (Armenti et al., 1994; Haugen et al., 1994; Pickrell et al., 1988; Williams et al., 1988; Bererhi et al., 1997). These patients can be treated by beta blocker, alpha-methyl dopamine, hydralazine or calcium blocker (Carosella 2009). Hypertension is responsible for pre eclampsia in 20 to 30% of cases in these patients (Levidiotis et al., 2009; Davison, 1995 ; Rizzoni et al., 1992; Armenti et al., 1994; Rudolph et al., 1979). In our study, a gravidic hypertension was observed in 3 cases, accompanied by a rise of the creatininemia in 1 case, a proteinuria in 2 cases and a hyperuricemia in 2 cases. Disturbances of the hepatic enzymes during pregnancy are frequent and due to multiple causes (Nicovani et al., 2009; Rahman and Wendon, 2002; Pereira et al., 1997). Infections particularly urinary tract infections are frequent in these patients (Bouattar et al., 2009; Caplan et al., 1970; Chaouat et al., 1989; Hamid 1986). Gestational diabetes occurs in 1 to 11% of cases in these patients (Levidiotis et al., 2009; Gutierrez et al., 2009). Vaginal is proposed in 1st intention in these patients (Penn et al., 1980). Acute rejection is similar or even lower than in general population (Armenti et al., 1994; Davison 1995 ; Framarino di Malat ta et al., 1993; Tanabe et al., 1997; Moritz 2002), in the absence of risk factors, which can explained anti-HLA antibodies made during and after the pregnancy (Cornella et al., 2009). We did not observe any case of acute rejection in our study. The incidence of the chronic graft dysfunction of the graft is also similar to the general population of the renal persons receiving a transplant when the creatininemia is lower than 150  $\mu\text{mol/l}$  (First et al., 1995; Rizzoni et al., 1992; Nojima et al., 1996; Thompson 2003). In our study, we observed only one case of chronic graft dysfunction explained by ciclosporine toxicity.

## Conclusion

Pregnancy in kidney recipient's patients is at high risk of fetal complications. It is reasonable to wait at least a period of 1 year after kidney transplantation to program a pregnancy, to have a normal blood pressure, a stable renal function (creatininemia < 1,50 mg /dl), absence of proteinuria and adapted immunosuppressive treatment. A multidisciplinary collaboration between nephrologist's transplants, gynecologists and podiatrists is mandatory.

## Conflict of Interest

The authors report no conflicts of interest.

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