

PREGNANCY AFTER RENAL TRANSPLANTATION: ARE GRAFT AND FETUS RISKS PREDICTABLE?

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Summary

We review 20 pregnancies in 18 transplanted patients with normal renal function to assess the incidence of graft rejection, fetal distress and failure to grow, and pre-pregnancy risk factors.

Three pregnancies were complicated by acute rejection during the third trimester and a further two by an abrupt deterioration of graft function during the first month post-partum progressing subsequently to chronic rejection. Signs of fetal distress, pre-term delivery and infant growth retardation were each about five times more frequent than in a control group.

Neither pregnancy associated rejection nor fetal complications were related to graft origin, time interval from transplantation to pregnancy, number of previous rejection episodes and blood pressure status prior to pregnancy.

Introduction

Pregnancy after renal transplantation involves a significant risk to both mother [1] and fetus [1-3]. In the present study we evaluate this risk and assess the prognostic value of several pre-pregnancy clinical characteristics on the outcome of pregnancy.

Material and methods

We selected from our patients those whose pregnancy led to a viable fetus (weight >500g) and who were delivered at our hospital.

Immunosuppressive drugs were continued throughout pregnancy, often at a slightly reduced dose (azathioprine 1-2mg/kg/day and prednisolone 4-15mg/day). Serum creatinine was followed monthly during the first two trimesters and bi-monthly during the last trimester. Fetal course was assessed by four parameters. Fetal growth retardation was diagnosed when transverse abdominal diameter measured by ultrasonography was below the 10th percentile for

TABLE I. Characteristics of mother and fetus (20 pregnancies in 18 transplanted patients)

Case ^o	Graft origin	T-P interval months	Before P		P associated rejection	oligo amnios	Fetal monitoring		P duration	Birth** weight (mg)
			serum creat. (mg/dl)	BP (mmHg)			meconium	IUGR hypoxia		
1	Cad	10	1.0	110/80	-	-	-	-	33	1980
2A	LR 1/2	13	0.8	130/95*	-	-	+	-	38	3800
2B		59	0.8	150/110*	+	-	-	+	37	2650
3	Cad	5	1.1	115/85*	-	-	+	-	39	2725
4	Cad	11	0.9	115/70	-	-	-	-	37	2570
5	Cad	22	1.0	100/60	-	-	-	-	34	2230
6A	LR 1/2	107	1.3	100/80	-	-	+	-	39	3400
6B		136	1.3	100/60	-	-	-	+	39	2770
7	LR 1/2	47	1.1	125/80*	-	-	-	+	37	2120
8	Cad	59	1.3	130/100*	+	-	-	+	36	1800
9	LR 1/2	54	1.3	125/85	+	-	+	+	30	650
10	LR 1/2	95	0.9	130/100	-	-	+	+	37	2360
11	Cad	19	1.3	130/90*	-	-	-	-	37	2545
12	LR 1/2	54	0.8	130/70	-	-	+	+	38	2540
13	LR 1/2	17	1.0	130/90	+	-	+	+	37	2045
14	Cad	11	1.1	130/95*	3° pp w	-	-	-	(?)	3750
15	Cad	6	1.1	115/85	32° P w	-	-	-	33	2200
16	Cad	43	1.4	110/85*	4° pp w	-	-	-	31	1350
17	LR 1/2	33	1.1	120/70	35° P w	-	+	-	35	2600
18	LR 2/2	59	1.3	125/80	31° P w	-	-	-	32	1830

^o = A,B indicate two pregnancies in the same recipient; P = pregnancy; T = transplantation; BP = blood pressure; IUGR = intra-uterine growth retardation (see material and methods); Cad = cadaver; LR = living related donor (1/2: haploidentical; 2/2: HLA-identical; * = with hypotensive therapy; P w = pregnancy week; pp w = post-partum week; ** = hypotrophic infants (see material and methods) are underlined

gestational age. Fetal hypoxia was diagnosed by established criteria on cardiotocographic recordings [4]. Oligohydramnios was diagnosed when amniotic fluid volume determined by ultrasounds decreased below 50 per cent of the normal volume for gestational age. Meconium emission was disclosed either by amnioscopy or at the time of membrane rupture. The frequency of these abnormalities in our transplant group was compared with that calculated in a control group of more than 5000 pregnancies observed at the same hospital during the same time interval. Infant growth retardation was defined by a birth weight for gestational age below the 10th percentile of the curve drawn from our control group.

Results (Table I)

There were 20 pregnancies in 18 transplanted patients. Mean age of the mothers at the time of conception was 28 (range 22–39) years. Graft originated from a cadaver in nine cases and from a living related donor in nine cases. Time elapsed from renal transplantation to conception varied from five to 136 (\bar{m} : 43) months and was below 24 months in nine cases. No rejection crisis had occurred before pregnancy in four cases whereas the sole (7) or the last (9) rejection episode had been successfully treated four to 128 (\bar{m} : 42) months before pregnancy in the 16 other cases. Before pregnancy, serum creatinine was ≤ 1.4 mg/dl in all cases, proteinuria was < 300 mg/day in all but one case (2B : 480mg/day), blood pressure was $\leq 135/90$ mmHg without hypotensive therapy in 11 cases and mildly elevated or normalized by hypotensive therapy in the others.

Graft function

Renal function remained normal throughout pregnancy up to the second month post-partum in 15 pregnancies. Graft rejection occurred in three pregnancies during the third trimester: in each of them biopsy disclosed signs of acute rejection superimposed on some chronic rejection. Deterioration of graft function attributed to rejection was encountered during the first month post-partum in two further pregnancies. In all cases, rejection was treated by IV methylprednisolone, associated during post-partum period with antilymphocyte serum.

The five cases with pregnancy associated rejection did not differ from the 15 other pregnancies according to the following pre-pregnancy parameters: graft origin (cadaver graft in 3/5 vs 6/15), time interval transplantation to pregnancy (< 24 months in 2/5 vs 7/15), blood pressure ($> 135/90$ or hypotensive therapy in 2/5 vs 7/15). Long-term graft function remained excellent in the majority of the 13 patients whose pregnancy was not complicated by rejection: 11 to 105 (\bar{m} : 45) months post-partum, serum creatinine is < 1.4 mg/dl in 11 of them, and between 1.5 and 2.5mg/dl in the two others. By contrast, none of the five patients having experienced pregnancy associated rejection maintained a good graft function: graft failure occurred in two cases (one complicated by fatal sepsis 69 months post-partum and the other leading to resumption of dialysis 28 months post-partum): in the three remaining patients, serum creatinine reached 1.8 to 3.5mg/dl, 10 to 56 months post-partum.

Fetal outcome

Intra-uterine growth retardation, fetal hypoxia, oligohydramnios and meconium emission were observed respectively in 40, 25, 20 and 45 per cent of the pregnancies, vs respectively 8, 2, 2 and 12 per cent in the control group ($p < 0.001$ for each parameter).

Pre-term delivery (before 37 weeks) occurred in 40 per cent of the pregnancies (vs 8% in the control group, $p < 0.001$) because of stillbirth (1 case) premature rupture of membranes (3 cases) or the need to induce delivery owing to either graft rejection (3 cases) or fetal hypoxia (1 case).

There was one stillbirth. Only one of the 19 liveborn infants was found to have a birth defect (atrio-ventricular block).

Eight pregnancies (40%) resulted in pre-term (2) or full-term (6) delivery of hypotrophic infants (vs 8% in the control population, $p < 0.001$). They did not differ from the other pregnancies leading to normal weight infants with regard to both time interval (transplantation to pregnancy < 24 months in 2/8 vs 7/12) and pre-pregnancy blood pressure ($> 135/90$ mmHg or hypotensive therapy in 4/8 vs 5/12).

Discussion

Our data demonstrate that pregnancy in transplanted patients is occasionally accompanied by an impairment of graft function: three of our patients experienced biopsy proven acute rejection between the 31st and 35th week of pregnancy, and a further two had an abrupt deterioration of graft function during the first month post-partum progressing subsequently to chronic rejection. This incidence of 25 per cent of pregnancy associated rejection is higher than the nine per cent rate reported in a large survey by Rudolph [1]. The reason for this difference is not clear. The small size of our series does not allow us to rule out a chance effect. Alternatively, the slight reduction in the immunosuppressive regimen often applied in our pregnant recipients might facilitate rejection during the third trimester of pregnancy. Even non-pregnant, our patients were at risk of rejection; it remains to be seen how much pregnancy increased this risk [5].

From a practical point of view, it is important to delineate what pre-pregnancy characteristic, if any, might predict the chances of pregnancy associated rejection. Unfortunately, neither graft origin, nor time interval from transplantation to pregnancy, nor blood pressure status, nor prior history of rejection, proved helpful in our series. Rudolph reached similar conclusions in his survey [1].

Our study is also concerned with fetal outcome. Signs of fetal distress are about five times more frequent in our patients than in a control population, a finding not yet reported by others. Moreover, we found a 40 per cent incidence of fetal growth retardation (assessed by ultrasonographic intra-uterine monitoring and birth weight for gestational age), a rate significantly higher than the eight per cent observed in our control population. This figure is difficult to compare with other series: indeed, Rudolph reports a 20 per cent incidence of prematurity defined by a shorter than 37 weeks pregnancy with a less than 2,500g

weight infant [1], whereas Fine reports a 50 per cent incidence of prematurity defined by infant weight without consideration of the duration of pregnancy [3]. In our patients, there was no relationship between prematurity and growth retardation: among the babies delivered prematurely (spontaneous or induced) 75 per cent were normal size whereas among the full-term deliveries 50 per cent of the newborns were small for dates.

It is noteworthy that graft rejection during pregnancy did not result in the delivery of small infants.

We also looked for pre-pregnancy predictive factors of growth retardation. None of our patients had marked renal insufficiency, pre-pregnancy serum creatinine being ≤ 1.4 mg/dl in all of them. Growth retardation was unrelated in our patients to the time interval transplantation to pregnancy a finding at variance with that reported by Cunningham [6]. Finally pre-pregnancy blood pressure status did not influence fetal outcome.

Taken together, our data do not disclose any pre-pregnancy risk factor for either graft rejection or growth retardation. It should be pointed out that this conclusion is valid only for transplanted patients with stable and satisfactory renal function without significant proteinuria. In this selected group, the more stringent pre-pregnancy criteria recommended by Davison [7] – time interval transplantation to pregnancy > 24 months and no significant hypertension – do not seem helpful to predict the outcome of pregnancy.

In pregnant renal transplant recipients with normal renal function and satisfactory blood pressure, the high risk as well as the lack of predictability of both graft alteration and fetal growth retardation require a careful monitoring by both the nephrologist and the obstetrician.

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