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IMPROVEMENT OF RENAL FUNCTION DURING PREGNANCY IN PATIENTS WITH A CADAVERIC RENAL ALLOGRAFT

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Summary

In a retrospective study the course of serum creatinine concentration and 24 hour creatinine clearance was investigated before, during and after nine pregnancies in eight renal allograft recipients. Creatinine clearance increased significantly throughout pregnancy with a concomitant fall in serum creatinine concentration. Creatinine clearance returned to pre-conception values one week before delivery. A negative correlation between the initial creatinine clearance and the percentage increase was observed. These data indicate the presence of a functional reserve capacity and the absence of a permanent state of maximal hyperfiltration.

Introduction

Glomerular hyperfiltration as a cause for progressive renal insufficiency is more likely in the presence of reduced renal mass [1]. Cadaveric renal transplant recipients with one kidney, potentially damaged by preservation procedures and rejection episodes, could suffer from permanent hyperfiltration. The presence of a renal functional reserve makes a permanent state of hyperfiltration unlikely. Normal human pregnancy leads to an increase of renal function [2]. Therefore we investigated the effect of pregnancy on the renal function in renal transplant recipients in order to collect evidence for the presence of renal functional reserve and indirect evidence for the absence of permanent hyperfiltration.

Patients and methods

In this retrospective study eight cadaveric renal transplant recipients have been studied during nine pregnancies. Some clinical data obtained before pregnancy are shown in Table I.

All patients were in a stable clinical condition before conception without urinary tract infection or urological abnormalities. Immunosuppression in all

TABLE I. Data of eight cadaveric renal allograft recipients before pregnancy

Pat. no. and age	Previous no. of grafts	Donor age	Tot. isch. time (hours)	Post Tx diuresis	Tx pregn. interval (months)	Ur. prot. excr. g/24h.	Bl.pr. mm Hg	A.H.D.
1. 33	0	19	30	immediate	40	0	125/80	none
2. 26	1	7	17	immediate	27	0	150/100	3
30					74	0.1	145/80	3
3. 28	1	46	19	immediate	32	0	130/80	2
4. 40	2	10	21	immediate	15	2.2	130/85	none
5. 25	0	8	23	immediate	48	0.3	110/80	none
6. 26	0	28	24	immediate	29	0.3	115/80	2
7. 31	0	14	18	immediate	41	0.4	135/85	none
8. 22	1	12	24	delayed	37	0.4	105/70	none

Tx=transplantation; AHD=anti-hypertensive drugs; 3=triple therapy consisting of diuretic, a betablocker and a vasodilator; 2=betablocker and diuretic

patients consisted of 10mg of prednisolone/day and 1.5mg of azathioprine/kg body weight/day. When the diagnosis of pregnancy was established, the azathioprine dose was reduced to 0.75–1.0mg/kg in patients Nos 1, 2, 5, 6 and 8. Physical examination and laboratory determinations were carried out every four weeks in the first trimester, every three weeks in the second and every one to two weeks throughout the third trimester of pregnancy. The reported observations were collected at 12, 24 and 32 weeks of gestation, representing the first, second and third trimester respectively. All pre-transplant data shown in the tables are the means of the last three pre-conception results. Creatinine in serum and urine was determined by the automated, modified Jaffé method. Urinary protein was determined by the biuret method. None of the patients was taking any medication with a known influence on creatinine metabolism or the determination technique of creatinine.

Results

The median values for serum creatinine and creatinine clearance before, during and after pregnancy are shown in Table II. The median pre-conception values were normal. A significant rise in creatinine clearance was observed during the first trimester ($p<0.02$), ongoing throughout the second and third trimester ($p<0.01$). During the second and third trimester the fall of the median serum creatinine became significant ($p<0.01$). The 24 hour creatinine and protein excretion both remained unchanged during the whole observation period. One patient with pre-conception asymptomatic proteinuria reached a maximum protein excretion of 3.9g/24hr without clinical problems. The median systolic

TABLE II. Data are expressed as median values (range)

	preconception	trimester 1st	trimester 2nd	trimester 3rd	post partum months 1st	post partum months 2-12th.
Se.cr. µmol/l	97 (76-108)	80 (72-115)	75^{xx} (53-90)	74^{xx} (61-90)	89 (65-105)	93 (71-95)
Cr.cl. ml/min.	80 (54-112)	91^{x} (71-118)	105^{xx} (96-134)	113^{xx} (104-125)	83 (63-125)	92 (75-110)
Cr.excr. mmol/24h.	12.0 (6.6-13.8)	11.8 (9.5-14.6)	12.4 (8.4-13.3)	12.7 (10.1-13.6)	11.6 (8.8-13.7)	11.7 (10.2-13.3)
Ur.pr.ex. g/24h.	0.1 (0-2.2)	0.2 (0-1.5)	0.2 (0-3.9)	0.2 (0-1.0)	0.1 (0-1.0)	0.1 (0-0.3)
Hct. %	42 (40-47)	38 (36-47)	34^{xx} (32-41)	34^{xx} (31-42)	35 (33-46)	41 (36-46)

$p < 0.01^{xx}$, $p < 0.02^{x}$.

Hct=haematocrit; ur.pr.ex=urinary protein excretion/24hr. Significance in relation to pre-conception data. Wilcoxon test

and diastolic blood pressure remained unchanged throughout pregnancy (data not shown). A significant fall in the haematocrit was observed during the second and third trimester ($p<0.01$). At one and two to 12 months after delivery the median creatinine clearance and serum creatinine returned to the pre-conception levels. The median haematocrit recovered only after two months post-delivery.

The course of the absolute creatinine clearance and the percentage increase in the creatinine clearance in the eight individual patients with nine pregnancies are shown in Table III. During all but one pregnancy an absolute and percentage increase in creatinine clearance occurred. The median percentage increases amounted to 15 per cent, 29 per cent and 51 per cent in the first, second and third trimester and were statistically significant in relation to the pre-conception values ($p<0.02$, $p<0.01$, $p<0.01$). The maximum creatinine clearance was reached during the third trimester with a relative narrow range (104–128ml/min). One week before each individual delivery the median creatinine clearance had already returned to the pre-conception level (85ml/min).

A negative correlation was observed between the initial creatinine clearance and the maximal percentage increase of creatinine clearance during the third trimester, $r = -0.82$, $p<0.02$ (Figure 1). However, no correlation could be demonstrated between the absolute creatinine clearances before conception and during the third trimester.

No rejection episodes or other complications related to the immunosuppressed status of the patients were observed. One case of mild pregnancy-induced

TABLE III. The absolute and percentage increase of the 24 hour creatinine clearance in eight renal allograft recipients during nine pregnancies. In the last column the creatinine clearance one week before delivery is shown. The median creatinine clearance amounts to 85ml/min, statistically not different from the pre-conception data

Pat. no.	Preconc. cr.cl. ml/min.	1st trimest. crcl	+ Δ %	2nd trimest. crcl	+ Δ %	3rd trimest. crcl	+ Δ %	last wk[x] cr.cl.
1.	84	85	1	107	26	110	29	85
2.	93	107	15	120	29	128	37	81
	105	127	20	105	0	104	0	83
3.	77	75	-3	96	24	113	51	58
4.	54	71	31	98	81	109	101	57
5.	112	118	5	134	19	121	8	114
6.	71	80	13	100	40	109	53	87
7.	78	91	16	103	32	121	55	85
8.	80	102	27	125	56	125	56	116
		median	16		29		51	
		$p < 0.02$		$p < 0.01$		$p < 0.01$		

p values in relation to pre-conception data. Wilcoxon test

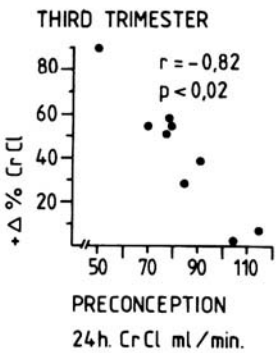

Figure 1. The correlation between the creatinine clearance before conception and the percentage increase of the creatinine clearance during the third trimester. r=Spearman-Rank corr. test

hypertension occurred. The median duration of pregnancies was 39 weeks, range 34–41 weeks. Six out of nine pregnancies ended by vaginal delivery, the remaining three by Caesarean section. The indications for the latter were: fetal growth retardation, aseptic femoral head necrosis and cephalopelvic disproportion.

The median birth weight was 2490g, range 1670–3930g. No neonatal problems occurred and no developmental abnormalities were found.

Discussion

In this retrospective study we found improved renal function as measured by serial determinations of serum creatinine and creatinine clearance. This increase was ongoing throughout pregnancy and was not caused by a rise of the median systolic or diastolic blood pressure and not accompanied with any changes in urinary protein excretion. As such, this observation points to the presence of a functional renal reserve capacity, as described after donor nephrectomy [3] and during protein intake [4]. A median increase in creatinine clearance to 29 per cent (range 0–81%) during the second trimester is in accordance with a recent prospective study [5]. The observation of the ongoing rise in creatinine clearance in the third trimester contradicts other reports in transplantation patients [5,6] and in normal pregnancy [7]. However, this contradiction is only a matter of timing, because creatinine clearances one week before delivery showed also in our patients a return to the 'normal' pre-conception levels. It has to be stressed, that a decrease of creatinine clearance at the end of the pregnancy in renal transplantation recipients is a physiological process and points more to an imminent delivery than to rejection.

We cannot completely support the statement made by others [5] that "the better the GFR before conception the bigger the percentage increment in pregnancy", although we do realize that creatinine clearance is not the same as GFR. We found that the percentage increase of creatinine clearance throughout pregnancy is the highest in the patients with the lowest initial creatinine clearance, a logical finding in the view of the narrow range of the maximal creatinine clearance at the third trimester. We could not explain this observation when we analysed either the data of the donor kidneys, or the age, body weight, blood pressure, proteinuria and haematocrit of the recipients. The assumption that the measured maximal creatinine clearance qas not an absolute maximum, but a range of renal function which is needed for the pregnancy, is not valid in view of the much higher creatinine clearance in normal pregnancies [2]. It could be possible that patients with a high pre-conception creatinine clearance do have, in fact, a limited form of hyperfiltration, while patients with a lower creatinine clearance have not.

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