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PREGNANCY AFTER KIDNEY AND KIDNEY-PANCREAS TRANSPLANTATION UNDER TACROLIMUS: A SINGLE CENTER'S EXPERIENCE

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Background. **Chronic renal failure leads to amenorrhea, and successful pregnancy is rare. The aim of the present report is to examine the outcome of pregnancies under tacrolimus after kidney transplantation (KTx) and simultaneous kidney-pancreas transplantation (SPKTx).**

Method. **All pregnancies under tacrolimus after KTx or SPKTx from 1993 to April 2002 were retrospectively examined. Renal function and the mother's survival were followed until December 2002.**

Results. **Thirteen mothers after KTx delivered 19 babies, and 2 mothers after SPKTx delivered 3 babies. All mothers survived the pregnancy and retained allograft function. One mother had a stillborn baby from an unrecognized amniotic fluid leak and a small ischemic placenta. The mean gestational period was 34.4±5.1 weeks. Mean birth weight was 2373±1001 g. Birth-weight percentile to gestational period was 40±28. None of the mothers experienced rejection during the pregnancy. Three pregnancies in mothers with KTx experienced toxemia of pregnancy, and one mother with SPKTx developed pre-eclampsia during both pregnancies. Five mothers (6 deliveries, 27.3%) required caesarian section. During the follow-up period, one mother died from a cerebrovascular accident. Another five mothers returned to dialysis**

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55.6±32.4 months after the last delivery and 99.4+28.5 months after the last KTx. Both SPKTx mothers have maintained normal renal and pancreatic allograft function 42 and 62 months postdelivery.

Conclusion. **All mothers survived the pregnancy. One baby was stillborn. Forty-one percent of babies were either preterm or premature, and 27% of babies were delivered by caesarean section. Toxemia of pregnancy or pre-eclampsia was observed in 23% of pregnancies postKTx and SPKTx. None of the mothers experienced rejection during their pregnancy.**

Chronic renal failure can often lead to amenorrhea, and successful pregnancy is rare. After successful kidney transplantation (KTx), pregnancy is possible. There are several reports of pregnancies after KTx under cyclosporine, azathioprine, and steroids (*1*, *2*). Although there are reports suggesting that tacrolimus is safer in pregnancy compared with cyclosporine after liver transplantation, in terms of less hypertension and toxemia of pregnancy (*3*, *4*), very little data are available on pregnancy after KTx under tacrolimus-based immunosuppression (*5*, *6*).

PATIENTS AND METHODS

All pregnancies between January 1993 to April 2002 under tacrolimus-based immunosuppression after KTx or simultaneous kidney-pancreas transplantation (SPKTx) were examined retrospectively. The course of pregnancy in the mother, changes in renal/pancreatic function and immunosuppression, gestational period, type of delivery, reason for caesarean section, birth weight, and presence of congenital anomalies were recorded. The birth-weight percentile for the gestational period was calculated using the Lubchenco et al. (*7*) chart. The survival of mothers and their allograft function were followed until December 2002.

RESULTS

Fifteen mothers (13 KTx and 2 SPKTx) delivered 22 babies (13 girls and 9 boys). One mother delivered three babies, and five mothers delivered twice. One mother (case 6) had an uneventful pregnancy course but delivered a stillborn baby at 32 weeks gestational period. This was thought to be related to an unrecognized amniotic fluid leak with a small ischemic placenta from renal impairment; however, 19 months later, she delivered a viable baby. Their primary diagnosis, interval to pregnancy from transplantation, gestational period, birth weight, birth-weight percentile for gestational period, along with the route of delivery, the reason for caesarean section, and the course of pregnancy are shown in Table 1. Two mothers received a living-related KTx, whereas the remaining 11 underwent cadaveric KTx. All mothers were on tacrolimus from the time of the KTx. Two patients (cases 4, 13) had more than one KTx before pregnancy. Two mothers (cases 7, 14) underwent SPKTx, and another mother (case 15) underwent combined retransplantation of the liver and kidney. Six mothers (cases 1, 4, 8, 9b, 11, 12) were on antihypertensive medications before pregnancy.

Allograft and Mother Survival

All 15 mothers survived the pregnancy and retained renal-allograft function during the pregnancy without requiring dialysis (all cases n=15). One mother (case 4), born with spina bifida, received her first KTx at the age of 14 years and her second KTx at 19 years of age. She delivered 50 months after the second KTx; 25 months after delivery (75 months after the second KTx), she lost the kidney to chronic rejection and returned to hemodialysis. She died 33 months later, after starting hemodialysis (58 months postdelivery and 97 months after the second KTx), of a cerebrovascular accident.

Course of Pregnancy after KTx

Three mothers (cases 3, 4, 14) developed toxemia of pregnancy. They presented with proteinuria and pedal edema in their third trimester. They all were managed medically. One of the mothers (case 11) also developed worsening hypertension with prolonged labor. She underwent caesarian section, whereas the other two delivered vaginally at 37, 27, and 37 weeks, respectively. One mother (case 5) was diagnosed with incontinence of the cervix during the first pregnancy. When she conceived a second time, at 19 weeks, she was managed by a cervical stitch with complete bed rest for 6 weeks, and labor was induced at the 25th week. Five more babies were delivered by caesarean section in 4 mothers (Table 1).

Course of Pregnancy after SPKTx

Two mothers (cases 7a, 7b, 14) delivered three babies. Mother 7 delivered twice. She developed pre-eclampsia during both pregnancies and presented with edema of the feet and proteinuria. She was managed medically, labor was induced, and the babies were delivered vaginally. Pancreatic function and renal function were well maintained during the entire pregnancy, and at last follow-up 62, 37, and 42 months postdelivery and 91 and 94 months postSPKTx.

Renal Function for All Mothers

Renal function in all 22 pregnancies during the entire period of pregnancy remained stable. There was an overall decrease in the serum creatinine from 1.38±0.47 prepregnancy to 1.19±0.47 in the first trimester, 1.13±0.44 in the second trimester, and 1.26±0.46 in the third trimester. Individual patients' serum creatinine in each trimester and at last follow-up are shown in Table 2. Five mothers (cases 2, 6, 8, 10, 13) lost renal function 26, 60, 98, 71, and 20 months (mean 55.6±−32.4) postdelivery and 56, 132, 107, 112, and 90 (mean 99.4±28.5) months posttransplantation, respectively. The mean serum creatinine in these five mothers before pregnancy was 1.6±0.7 (median 1.6, range 0.9–2.8) mg/dL, whereas the mean serum creatinine in mothers who retained renal function was 1.25±0.3 (median 1.3 range 0.9–1.7) mg/dL .

Gestational Period

The mean gestational period for all 22 deliveries was 34.4±5.1 (median 36.5, range 24–40) weeks. Nine (40.9%) babies were born with less than 36 weeks of gestational period, and five (23.8%) with less than 30 weeks (Table 1).

Birth Weight

The mean birth weight for the 21 viable babies was 2,373±1,011 (median 2,386, range 540–4,261) g. Six (28.6%) babies were less than 2,000 g, and two (9.5%) were less than 1,000 g (Table 1).

Birth-Weight Percentile for the Gestational Period

The mean birth-weight percentile for the 21 viable newborns was 40±28 (median 34, range <10 to >90). Thirteen

TABLE 1. Kidney and pancreas patients

Mother no.	Baby no.	Diagnosis	Transplant organ	Gestational period (weeks)	Age at delivery (yrs)	Months from KTx to delivery	Birth-weight percentile	Birth weight (g)	Boy/ girl	Vaginal/ caesarian section	Reason for caesarian section	Pregnancy course
1[a]	1	Pyelo nephritis	Kidney	35.5	31.10	11.74	37.5	2216	Boy	Vaginal		
2[b]	2	Diabetes mellitus	Kidney	38	33.95	30.77	40	3125	Girl	Vaginal		
2b[b]	3			32	35.86	53.62	60	1790	Boy	Vaginal		
3	4	Systemic lupus	Kidney	39	38.10	42.64	80	3750	Boy	Vaginal		3 g proteinuria at 31 weeks
4[a]	5	nephropathy; spina bifida	Kidney	27	23.47	50.39	<10	710	Girl	Vaginal		Eclampsia with rise in liver function and hypertension
5	6			28	28.72	26.04	>90	2216	Girl	Vaginal		Incontinent cervix
5b	7	Cong. Pyelo nephritis	Kidney	25	32.08	66.47	<10	1051	Boy	Vaginal		Stitch-x-2; incontinent cervix labor 18.5 wks, bed rest complete 7.5 wks
6	8	Glomerulo nephritis	Kidney	32	28.48	53.98			Boy	Vaginal		Stillborn baby, small ischemia of placenta with amniotic leak
6b	9			36	29.97	71.83	30	2159	Boy	Vaginal		
7[c]	10	Diabetes mellitus	Kidney + pancreas	32	36.87	29.36	50	1619	Boy	Vaginal		Pre-eclampsia labor induced
7b[c]	11			37	38.92	54.01	60	3068	Girl	Vaginal		Pre-eclampsia labor induced
8[a]	12	Focal segmental glomerulo sclerosis	Kidney	38	29.59	14.66	25	2386	Girl	Caesarian section	Prolong labor	
9	13	Focal segmental glomerulo sclerosis	Kidney	39	34.05	24.62	>90	4261	Girl	Caesarian section	Breach presentation	
9b[a]	14			39	36.46	53.58	75	3750	Girl	Caesarian section	Previous caesarian section	
10	15	Glomerulo nephritis	Kidney	24	25.14	41.45	<10	540	Girl	Vaginal		
10b	16			40	28.00	62.00	<10	2443	Girl	Vaginal		
10c	17			38	30.00	76.00	37	2869	Boy	Caesarian section	Cord prolapsed	
11[a]	18	Poststreptococcal glomerulo nephritis	Kidney	37	26.47	84.45	30	2727	Girl	Caesarian section	Prolong labor, hypertension, edema	Pre-eclampsia
12[a]	19	Systemic lupus	Kidney	37	40.37	66.17	30	2329	Girl	Vaginal		
13	20	Reflux nephropathy	Kidney	40	29.32	69.66	15	2784	Girl	Caesarian section	Prolong labor	
14[c]	21	Diabetes mellitus	Pancreas	28	38.94	52.40	<10	1023	Boy	Vaginal		
15[d]	22	Drug induced	Kidney	36	33.08	68.97	75	3011	Girl	Vaginal		
Mean				34.4	32.23	50.22	40	2373				
SD				5.1	4.79	20.33	28	1001				
Median				36.5	31.59	53.60	34	2386				

[a] Hypertensive.
[b] Diabetic.
[c] Kidney and pancreas transplant.
[d] Also received two liver transplants.
KTx, kidney transplant.

TABLE 2. Renal function

Mother no.	Baby no.	Before pregnancy		First trimester		Second trimester		Third trimester		Last Follow up December 2002		
		BUN	CREAT	BUN	CREAT	BUN	CREAT	BUN	CREAT	Months postKTx	Months postdelivery	Renal function/creatinine/dialysis
1	1	21	1.5	18	1.3	20	1.5	18	1.7	86.57	74.84	2.1
2	2	34	1.7			16	0.9			81.05	50.31	Began dialysis 26 months post first and 3 months post second delivery
2b	3									81.05	27.49	
3	4	29	1.6	26	1.5	25	1.6	19	1.6	110.31	67.72	1.8
4	5	22	1.2	16	1.4	22	1.3	20	1.3			Died, see text
5	6	16	1.5	16	1.2	15	1.3	13	1.2	128.90	102.89	1.3
5b	7	18	1.3	12	0.8	11	1	13	1.2	128.90	62.50	
6	8	22	2	23	1.8			21	1.8	124.85	53.09	Began dialysis 60 months post second delivery
6b	9	29	2.8	40	2.4	31	2.2	29	2.3	143.02	71.26	
7	10	14	0.9	12	0.8	12	0.7	9	0.9	91.36	62.04	1.0
7b	11	11	1.1	10	0.7	9	0.9	8	0.9	91.36	37.41	
8	12	12	0.9	8	0.6	8	0.6	11	1.1	125.22	110.57	Began dialysis 98 months postdelivery
9	13	14	0.9	12	0.8	10	0.6	10	0.7	82.92	58.33	0.8
9b	14	11	0.6	12	0.6	8	0.6	10	0.6	82.92	29.39	
10	15	20	1.6	14	1.6	9	1.3	8	1.3	127.16	112.58	Began dialysis 98 months post first and 52 months post third delivery
10b	16	27	1.3		1.6					127.16	85.75	
10c	17	15	1.6			20	1.4	16	1.7	127.16	67.16	
11	18	23	1.4	21	1.2	17	1.2	16	1.1	155.80	71.43	1.5
12	19	14	0.9	13	0.8	11	0.9	10	0.8	103.97	37.87	1.1
13	20	17	1.2	12	0.9					105.39	35.80	Began dialysis 20 months postdelivery
14	21	29	1.5	25	1.5					93.99	41.64	1.3
15	22	23	1.4	20	1.1	13	1	21	1.3	77.70	8.80	1.1
Mean		20.05	1.38	17.22	1.19	15.25	1.13	14.44	1.26	107.60	60.79	
SD		6.72	0.47	7.73	0.47	6.81	0.44	5.84	0.46	23.67	28.14	
Median		19.00	1.35	14.00	1.20	13.50	1.10	13.00	1.20	105.39	62.50	

BUN, blood urea nitrogen mg/dL; CREAT, Serum creatinine mg/dL.

(61.9%) were below the 50th percentile for the given gestational period, six (28.6%) were below the 25th percentile, and five (23.8%) were below the 10th percentile. All 21 babies are alive and well at last follow-up.

Rejection / Immunosuppression

Although there was a considerable decrease in tacrolimus trough levels, with the increase in body volume during the pregnancy, the dosage of tacrolimus was not increased. Acute rejection was not seen during pregnancy, and patients did not require any additional treatment.

Four mothers were on a small dose of prednisone at 2.5 to 7.5 mg per day. In most cases, it was reduced during the pregnancy. Three mothers (cases 7a, 7b, 14, 15), were on azathioprine, 75 to 100 mg per day, and it was continued during all three pregnancies.

Patient 12 was on mycophenolate mofetil before pregnancy; it was discontinued when the pregnancy was confirmed. Details of immunosuppression are shown in Table 3.

Congenital Anomaly

All viable babies were normal, and no congenital anomaly was detected in any of the babies. An autopsy was not performed on the stillborn baby; however, no external anomaly was observed.

DISCUSSION

In the past, we reported the largest single-center experience of pregnancy after liver transplantation under tacrolimus, with satisfactory outcomes, which has been confirmed by others (*8*, *9*). Either small case studies or review articles are available on pregnancy after SPKTx (*10*, *11*).

Excluding our brief citation on pregnancies in renal transplantation under tacrolimus (*12*), this is the first report on a large series of pregnancies under tacrolimus after KTx from a single center. Although all mothers survived and maintained allograft function, one baby was stillborn at 32 weeks gestation. She delivered a viable baby 19 months later.

There are several reports of successful pregnancies after KTx under azathioprine and cyclosporine (*1*, *2*). Preterm delivery and premature delivery with low birth weight and intrauterine growth retardation have been the common problems in immunosuppressed mothers. A pre-eclampsia rate of approximately 30% has been reported under cyclosporine for KTx patients. In the present series, the pre-eclampsia rate was 13.6% for the KTx patients. In the three SPKTx pregnancies, one mother experienced pre-eclampsia during both pregnancies, whereas the other mother did not. Rejection during pregnancy is a rare phenomenon under cyclosporine, but postpartum rejection and deterioration in renal function

TABLE 3. Immunosuppression

Mother no.	Baby no.	Before pregnancy				First trimester				Second trimester				Third trimester			
		Tacro. dose (mg)	Tacro. level (ng/mL)	Pred. dose (mg/dL)	Aza. (mg/day)	Tacro. dose (mg)	Tacro. level (ng/mL)	Pred. dose (mg/dL)	Aza. (mg/day)	Tacro. dose (mg)	Tacro. level (ng/mL)	Pred. dose (mg/dL)	Aza. (mg/day)	Tacro. dose (mg)	Tacro. level (ng/mL)	Pred. dose (mg/dL)	Aza. (mg/day)
1	1	10 BID	11.5	7.5	0	10 BID	6.6	2.5	0	12 BID	6	0	0	10 BID	5.9	0	0
2	2	6 BID	12.3	2.5	0	6 BID		0	0	1 BID	<5	0	0			0	0
2b	3	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
3	4	4 BID	11.5	5	0	4 BID	8.2	5		4 BID	8.4	5		4 BID	7.6	5	
4	5	6 BID	11.5	0	0	6 BID	ND	0	0	6 BID	ND	0	0	6 BID	NL	0	0
5	6	2 BID	0.4	0	0	2 BID	0.2	0	0	2 BID	0.1	0	0	2 BID	<.5	0	0
5b	7	2 BID	10.8	0	0	2 BID	4.5	0	0	2 BID	3.1	0	0	2 BID	NL	0	0
6	8	5 BID	8			5 BID				5 BID	8			5 BID			
6b	9	4 BID	5.6	0	0	4 BID	NL	0	0	4 BID	6.8	0	0	4 BID	6.9	0	0
7	10	2 BID	12.7	0	100	2 BID	4.2	0	100	2 BID	5.2	0	100	2 BID	7.4	0	100
7b	11	2 BID	9.5	0	100	2 BID	8.7	0	100	2 BID	7.9	0	100	2 BID	8.2	0	100
8	12	8 BID	0.4	5	0	8 BID	0.3	2.5	0	8 BID	0.3	2.5	0	8 BID	0.6	0	0
9	13	5 TID	7.9	0	0	5 TID	5.8	0	0	5 TID	4.1	0	0	5 TID	4.8	0	0
9b	17	5 TID	7	0	0	5 TID	4.3	0	0	5 TID	5.1	0	0	5 TID	4	0	0
11	18	3 BID	8.9	0	0	3 BID	ND	0	0	3 BID	ND	0	0	3 BID	ND	0	0
12	19	5+4	ND	0	0	4+3	ND	0	0	4+3	ND	0-Jan	0	4+3	ND	0	0
13	20	4+3	9.1	0	0	4+3	7.9	5	0	4+3	ND	5	0	4+3	ND	0	0
14	21	3 BID	5.9	0	75	3 BID	0	0	75	3 BID	ND	0	75	3 BID	ND	0	0
15	22	2 BID	5.7	10	75	2 BID	7.9	10	75	2 BID	6.6	10	50	2 BID	6.6	0	0
		8.59	8.67	1.25		8.72	4.61	0.94		8.50	5.00	0.78		8.35	5.68	0.31	
		5.42	5.27	2.42		5.19	3.25	1.80		5.81	2.89	1.76		4.90	2.51	1.25	
		7.50	8.00	0.00		8.00	4.50	0.00		7.00	5.20	0.00		7.50	6.40	0.00	

Pt 10 information not available; Pt 12 on mycophenolate mofetil 500 mg/day, discontinued in first trimester when pregnancy was confirmed.
Tacro, tacrolimus; Pred, prednisone; Aza, azathioprine, n/a, not available; ND, not done; BID, twice a day; TID, three times a day.

has been observed. In this series with tacrolimus, we did not observe any episode of rejection during pregnancy, although there was a reduction in prednisone dosage and a decrease in the tacrolimus concentration by nearly 32%.

There was no increase in serum creatinine during the pregnancy. However, five (38%) mothers lost renal-allograft function 20 to 98 months postdelivery and 56 to 132 months posttransplantation. The impact of pregnancy on graft loss is difficult to evaluate, but the high rate of graft loss is clearly of concern. This observation is also different than what is observed in pregnancies after liver transplantation under tacrolimus (*10*, *11*).

Pregnancy after SPKTx has been previously reported. In this series, there were three deliveries in two mothers; one mother delivered twice and experienced pre-eclampsia on both occasions. She was managed medically and delivered successfully. Both mothers maintained pancreatic and renal function 42 to 62 months after the first delivery.

CONCLUSIONS

Pregnancy after KTx and SPKTx under tacrolimus-based immunosuppression has the same problems of prematurity, preterm delivery with low birth weight, and intrauterine growth retardation that have been observed with pregnancy after transplantation with other immunosuppressive agents. Although impaired renal function at the time of pregnancy should be considered an important risk factor, toxemia of pregnancy, deterioration of allograft function, or rejection were relatively rare during pregnancy.

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CRITICAL EVALUATION OF THE AMINO ACID TRIPLET-EPITOPE MATCHING CONCEPT IN CADAVER KIDNEY TRANSPLANTATION

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Background. **A computer-based approach for determining human leukocyte antigen (HLA) compatibility between kidney donors and recipients on the basis of differences of amino acid sequences as motifs for immunogenic epitopes was proposed by Duquesnoy et al. The HLAMatchmaker algorithm focuses on HLA class I polymorphisms of serologically defined antigens encoded by the HLA-A and -B loci. HLA phenotypic mismatches that represent only a few mismatches at the amino acid triplet level are held to be not or only mildly immunogenic. This approach was proposed as being especially suitable for the allocation of donor kidneys to highly sensitized patients.**

Methods. **We reexamined this attractive concept using the data of the Collaborative Transplant Study. Intra- and interlocus comparisons for HLA-A and -B were performed according to the original HLAMatchmaker algorithm. To exclude the influence of HLA-DR, only transplants with no HLA-DR mismatch were considered. Patients who had one HLA-A and one HLA-B antigen mismatch were separated into subgroups, depending on the number of triplet mismatches as calculated by the HLAMatchmaker software. Separate**

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