

## Original Article

# Pregnancy in women receiving renal dialysis or transplantation in Japan: a nationwide survey

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### Abstract

**Background.** Since a report on the first successful pregnancy of a woman on long-term haemodialysis in Japan in 1977, there has been a growing number of case reports on successful pregnancy in patients on dialysis. We undertook a nationwide survey on pregnancy in women on renal replacement therapy in 1996. **Methods.** A preliminary questionnaire was sent to 2504 dialysis units and 143 renal transplant units in Japan. For each reported pregnancy, a more detailed questionnaire was sent to collect nephrological, obstetric and neonatal information.

**Results.** There were 172 pregnancies (0.44%) reported in 38 889 women on dialysis, with 90 successful pregnancies (0.23%), and 194 pregnancies reported in 852 female renal transplant recipients. Detailed pregnancy information was collected from 74 women on dialysis and 194 renal transplant recipients. Of the 74 pregnancies in the women on dialysis, 36 (48.6%) resulted in surviving infants, nine (12.2%) in neonatal death, nine (12.2%) spontaneous abortions and 14 (18.9% elective abortions were reported. The outcome of six pregnancies (8.1%) was unknown. Of 194 pregnancies in renal transplant recipients, 159 (82.0%) resulted in surviving infants, two (1.4%) in neonatal death and 28 (14.4%) in spontaneous or elective abortion. In five cases the pregnancy outcome was not reported. No congenital anomalies were reported, except two infants with mental retardation and one with epilepsy.

**Conclusion.** The current survey revealed that the rate of successful pregnancy in women on dialysis has improved. More than half of the pregnancies resulted in infant survival. But, premature birth is a major problem for the children of women on dialysis and there is a higher rate of neonatal death. There are significant differences in gestational age, birth weight, frequency and severity of prematurity and rates of neonatal death between pregnancies of women undergoing dialysis and those who are renal transplant recipients.

**Key words:** dialysis; pregnancy; renal transplantation

### Introduction

It is well known that women with end-stage renal disease (ESRD) are usually amenorrhic or have irregular anovulatory menstrual cycles and consequently are infertile. The first description of conception and successful delivery in a woman on maintenance haemodialysis was by Confortini *et al.* [1] and further individual case reports followed [2–9]. However, few studies allow an accurate evaluation of the frequency of gestation and its outcome in the whole population of women on dialysis. The first successful pregnancy in Japan of a woman on long-term haemodialysis was reported in 1977 [2]. In the first Japanese nationwide survey on the frequency and outcome of pregnancy, which was carried out in 1981, there were 78 pregnancies (0.8%) in 9912 women on dialysis, with six (9%) successful pregnancies, 50 (64%) elective abortions and 21 (27%) spontaneous abortions.

Since that time, there has been not only an enormous increase in the number of patients on maintenance dialysis but also great progress in the management of dialysis patients, including the widespread use of hiflux dialysis membranes, continuous ambulatory peritoneal dialysis (CAPD) and the introduction of erythropoietin for the treatment of anaemia. At the end of 1996, the total number of patients in Japan treated using dialysis was 167 192, while the number treated by kidney transplantation was 9600. This has resulted in a growing number of case reports on successful pregnancy in dialysis patients. Therefore, in 1996 we undertook the second Japanese nationwide survey on pregnancy in female dialysis patients and the first on pregnancy in female renal transplant recipients.

### Methods

A preliminary questionnaire was sent to the directors of 2504 dialysis units and 143 renal transplantation units in Japan.

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The questionnaire asked for the number of women treated in the units, the number of pregnancies and their clinical outcome. When a pregnancy was reported, a more detailed questionnaire was sent to determine the nature of the underlying renal disease, the length of time on dialysis, mode of dialysis, dialysis regimen, blood pressure control and the use of erythropoietin for anaemia. Obstetric and neonatal information was collected on obstetric regimen and occurrence of obstetric and neonatal problems including premature labour, polyhydramnios, the need for caesarian section and neonatal complications. Outcomes were defined as follows [7]: *surviving infants*, infants who were alive at discharge from the hospital; *neonatal death*, death before discharge from the hospital or within the first month of life; *stillbirth*, intrauterine foetal death after the first trimester and before the onset of labour; and *spontaneous abortion*, delivery of a foetus alive at the onset of uterine contractions before 20 weeks' gestation. Elective abortions were performed for anticipated medical problems or for social reasons.

In transplanted recipients, additional information was collected on length of time after transplantation, immunosuppressive regimen, and graft function before and after pregnancy.

The analyses were performed using the SAS system (SAS Institute Inc., Cary, NC, USA). The data were presented as frequency or means  $\pm$ SD. Chi-square or Fisher's exact probability test was applied for categorical data. Unpaired *t*-test was used to test for statistically significant difference between two continuous variables. When the group variances were not assumed to be equal, Welch's *t*-test was applied. Two-tailed *P*-values of less than 0.05 were considered to indicate statistical significance.

## Results

### *Pregnancy in women on maintenance dialysis*

**Frequency of conception.** The 1712 units (64.6%) responding to the first questionnaire listed 38 889 women on dialysis and 852 female renal transplant recipients; 110 dialysis units reported experience with pregnant women: 172 pregnancies and 90 successful pregnancies. The Registration Committee of The Japanese Society for Dialysis Therapy reported that the total number of female patients treated in Japan with dialysis at the end of 1996 was 66 552, of which 8556 were between the ages of 15 and 44 years receiving dialysis. Proportionally, in 38 889 female dialysis patients treated in 1712 units, 5000 were estimated to be between the ages of 15 and 44 years. The conception rate was approximately 3.4% for the haemodialysis patients in Japan.

**Outcome of pregnancy.** More detailed information was collected from 57 dialysis units (51.8%) on 74 pregnancies (43%) in women on maintenance dialysis. Pregnancy outcome was known for 68 of the 74 pregnancies (Figure 1). Thirty-six (48.6%) resulted in surviving infants, nine (12.2%) in neonatal death, nine (12.2%) in spontaneous abortions and 14 (18.9%) in elective abortions. The spontaneous abortions occurred at a mean of  $15.3 \pm 7.2$  weeks of gestation. Elective abortions were performed for anticipated medical

problems or social reasons at a mean of  $13.1 \pm 6.3$  weeks of gestation.

**Dialysis modality and length of time on dialysis.** All pregnancies occurred in women on maintenance haemodialysis. Mean age at gestation was  $32.7 \pm 5.0$  years, and the length of time on dialysis prior to conception was 0.6 to 25 years (mean:  $8.0 \pm 5.6$  years); 19 pregnancies (25.6%) occurred in women treated with maintenance haemodialysis for more than 10 years. Of these, nine (47.4%) resulted in surviving infants, four (21.1%) in neonatal death, three in spontaneous abortion and three in elective abortion. There is no difference in pregnancy outcome in women on dialysis for more than 10 years or less.

**Dialysis regimen.** After conception was confirmed, serum urea was kept below 21 mmol/l and serum creatinine less than 531  $\mu$ mol/l by increasing in the duration and frequency of dialysis. The mean dialysis time of 48 pregnant women was 22 h per week (range: 18–24 h). The frequency of dialysis was 3–6 times a week, with a mean frequency of 4.5 times a week. Thirty-four patients (70.8%) were treated with erythropoietin to maintain a haematocrit higher than 25%.

**Complications of pregnancy.** Threatening premature uterine contraction occurred in 38 (84.4%) of 45 deliveries, polyhydramnios in 24 (53.3%) and severe hypertension during pregnancy in 19 (42.2%).

Most of the pregnant women on haemodialysis required hospitalization at around 20 weeks of gestation, mainly to treat threatening premature contraction.

**Gestational age.** Mean gestational age was  $31.9 \pm 4.5$  weeks (range: 23–38.7 weeks). Thirty-nine (86.7%) of 45 newborn infants were born before 37 weeks of gestation (Figure 2). Twelve (27.9%) infants were born with a mean birth weight of 790.8g before 28 weeks of gestation (Table 1). Seven (58.3%) of them died within 3 days after birth due to prematurity. Five infants under 28 weeks of gestation survived, but four of them had severe foetal complication such as respiratory distress syndrome, cerebral palsy and premature retinopathy. The incidence of major foetal complications obviously decreased in infants of more than 32 weeks of gestation ( $P=0.034$ ). The causes of premature delivery were threatening premature uterine contraction in 50%, foetal distress in 31.3%, and intrauterine growth retardation in 18.7%.

**Foetal complications.** The mean birth weight was  $1543.5 \pm 671.9$ g (range: 530–2856g) and the average Apgar score was  $6.3 \pm 2.7$ . Forty-two (93.3%) of 45 newborn infants were below 2500 g in birth weight and 14 infants (31.1%) were below 1000g in birth weight, with a mean birth weight of  $739.4 \pm 136.7$ g (Table 1). Nine (64.3%) of these died 6 h to 120 days after birth, mainly because of respiratory distress syndrome. Even if surviving, every infant whose birth weight was less than 1000 g had severe foetal complications such as respiratory distress syndrome, premature retinopathy, cerebral palsy and mental retardation. Compared with surviving infants (Table 2), the dead neonates were significantly younger in gestational age ( $26.2 \pm 2.7$

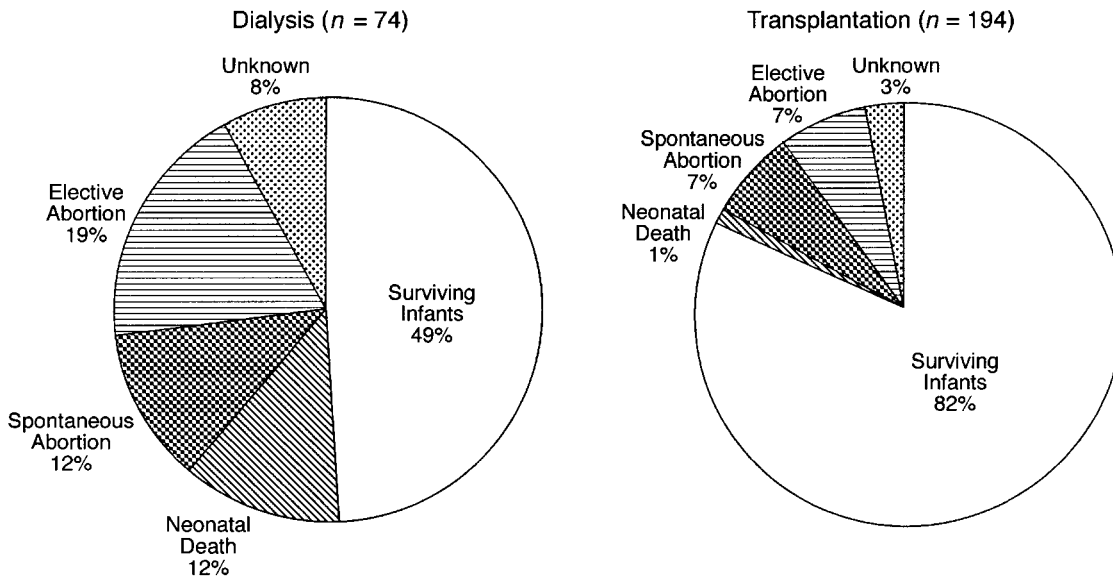


Fig. 1. Outcome of pregnancy in women on renal replacement therapy in Japan.

### Gestational Age and Fetal Outcome

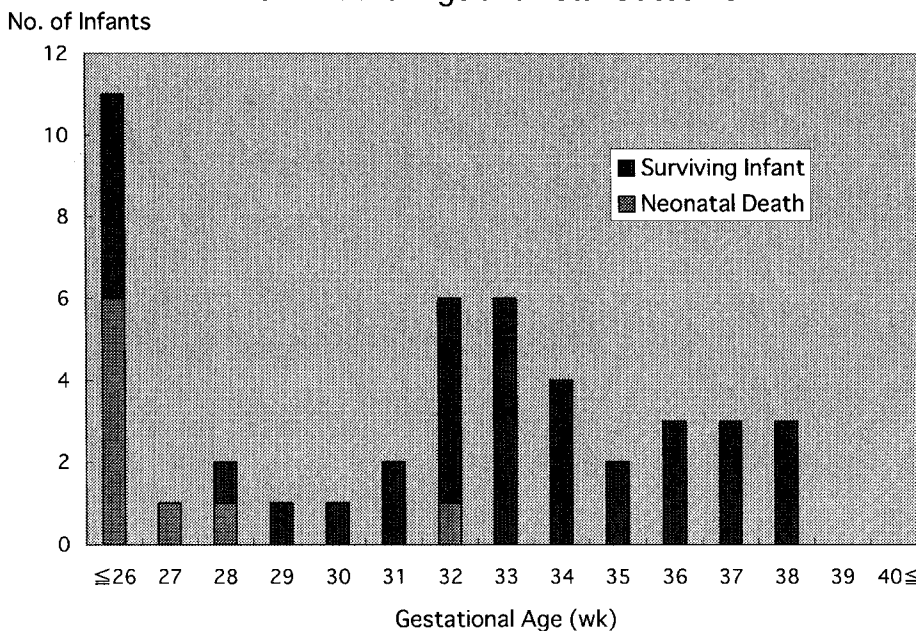


Fig. 2. Gestational age and foetal outcome in women on haemodialysis.

weeks vs  $32.8 \pm 3.8$  weeks;  $P = 0.023$ ) and lower in birth weight ( $700.5 \pm 144.5$ g vs  $1725.8 \pm 596.4$ g;  $P < 0.001$ ). All the infants that died were born less than 1000 g in birth weight. Other complications of newborn infants were premature retinopathy (8.9%), neonatal jaundice (8.9%), atrial septal defect (ASD; 4.4%), cerebral palsy (4.4%) and cerebral atrophy (4.4%).

#### Pregnancy in female kidney transplant recipients

Information was collected from 130 of the 143 transplantation units (91%). These units cared for 852

female recipients. The outcome of pregnancies was known in 189 women with a functional kidney graft (Figure 1). One hundred and fifty-nine (82.0%) resulted in successful pregnancies, 28 (14.4%) in spontaneous or elective abortion and two (1.0%) died in the perinatal period due to prematurity. The women's mean age at gestation was  $31.2 \pm 4.6$  years, and the interval after kidney transplantation was 12–177.5 months, with a mean interval of 58.7 months (4.9 years). Most of the women (85.7%) were given a kidney graft from a living related donor, and the rest (14.3%) from cadavers. The mean number of

**Table 1.** Gestational age and birth weight of neonatal infants

	<i>n</i> (%)	Surviving infants	Neonatal death	Major foetal complication
<b>Gestational age (weeks)</b>				
<28	12 (26.7)	5*	7*	4/5 (80.0%)**
28–32	6 (13.3)	5*	1*	4/5 (80.0%)**
32–37	21 (46.7)	20*	1*	5/20 (25.0%)**
37 ≤	6 (13.3)	6*	0*	2/6 (33.3%)**
<b>Birth weight (g)</b>				
<1000	14 (31.1)	5†	9†	5/5 (100%)‡
1000–1500	9 (20.0)	9†	0†	3/9 (33.3%)‡
1500–2500	19 (42.2)	19†	0†	6/19 (31.6%)‡
>2500	3 (6.7)	3†	0†	1/3 (33.3%)‡
	45	36 (80.0%)	9 (20.0%)	15/36 (41.7%)

\* $P < 0.001$ , \*\* $P = 0.034$ , † $P < 0.001$ , ‡ $P = 0.043$ .

**Table 2.** Comparison of gestational age and weight between surviving infants and neonatal deaths

	Surviving infants ( <i>n</i> = 36)	Neonatal deaths ( <i>n</i> = 9)	<i>P</i> -value
<b>Gestation age (weeks)</b>			
<28	32.8 ± 3.8	26.2 ± 2.7	0.023
<28	5 (13.9%)	7 (77.8%)	<0.001
<b>Birth weight (g)</b>			
	1725.8 ± 596.4	700.5 ± 144.5	<0.001

mismatched HLA antigens was  $2.48 \pm 1.02$ , and four kidneys were transplanted from ABO-blood group incompatible donors.

Of 194 pregnant women with a functional graft, 100 (51.5%) received a maintenance dose of cyclosporin-based immunosuppression, 73 (37.6%) conventional azathioprine-based treatment and one FK506-based immunosuppression. Immunosuppressive regimens were not reported in 20 (10.3%) women. One hundred and forty six (90.7%) had no proteinuria at conception and the kidney graft function prior to conception was stable with a mean serum creatinine concentration of  $100 \pm 30 \mu\text{mol/l}$  and a mean creatinine clearance of  $59.0 \pm 21.0 \text{ ml/min}$ .

The major complications during pregnancy were pre-eclampsia in 38 women (23.9%), threatening premature contraction in 31 (19.3%) and deterioration of graft function in 30 (19.2%). In nine (30%) of 30 patients, deterioration of the graft function prolonged after delivery and four patients (13.3%) resulted in the graft loss. The immunosuppressive regimen had to be changed during pregnancy in 34 cases (20.4%).

Gestational age was reported for 144 infants. The mean gestational age at delivery was  $35.7 \pm 3.2$  weeks. Preterm delivery occurred in 85 (59.1%), and 59 (40.9%) pregnancies reached term. Three (2.1%) infants were born at less than 28 weeks of gestation. Premature deliveries were caused by premature labour in 14 (25.5%), foetus distress in 14 (25.5%), severe hypertension in 13 (23.6%), deterioration of graft function in nine (16.4%) and intrauterine growth retardation in five women (9.1%).

Mean birth weight was  $2360.1 \pm 605.3 \text{ g}$  (range: 623–3595g) and mean Apgar's score was  $8.1 \pm 1.9$ . Low-weight infants less than 2500 g at birth numbered 83 (54.6%). While mean birth weight of 57 infants born to patients receiving conventional azathioprine-based immunosuppression was  $2567 \pm 491.1 \text{ g}$ , that of 94 infants born to women with cyclosporin-based immunosuppression was  $2252 \pm 629.2 \text{ g}$  [3,4]. This was a significant difference ( $P < 0.001$ ). All of infants with extremely low birth weight less than 1000 g were born to cyclosporin-treated mothers.

One hundred and fifty-nine newborn infants survived but two (1.0%) neonatal deaths were reported. Serious congenital malformations were not reported except in five newborns (2.6%). Each of these five infants had a different complication: patent foramen ovale, congenital hydronephrosis, ventral hernia, undescend testis and polydactyly.

The kidney graft function following successful pregnancy was reported in 133 patients. The mean plasma creatinine was  $162 \pm 166 \mu\text{mol/l}$  (range: 45–1133  $\mu\text{mol/l}$ ) at 6 months or longer after delivery. Proteinuria was reported in 35 of 115 patients (30.4%). In 31 (23.3%) patients, the graft function decreased after labour; 13 of them (9.7%) lost a kidney graft; in eight of these (61.5%) the graft loss occurred within 3 years of the pregnancy, while in five (38.5%) it occurred more than 10 years after delivery (Figure 3). In the former group, graft survival may have been affected by the pregnancy.

## Discussion and conclusion

It has been considered that the perinatal and infant outcome in women on maintenance dialysis is poor. In 1980, the EDTA Registration Committee reported that successful pregnancy in women treated with chronic dialysis was only 23% of 115 pregnancies [5]. In 1981, the first Japanese nationwide survey on the frequency and outcome of pregnancy in women on dialysis revealed that only six (9%) of 78 pregnancies resulted in live births. In 1992, Souqiyeh *et al.*

## Time length to graft loss after labor

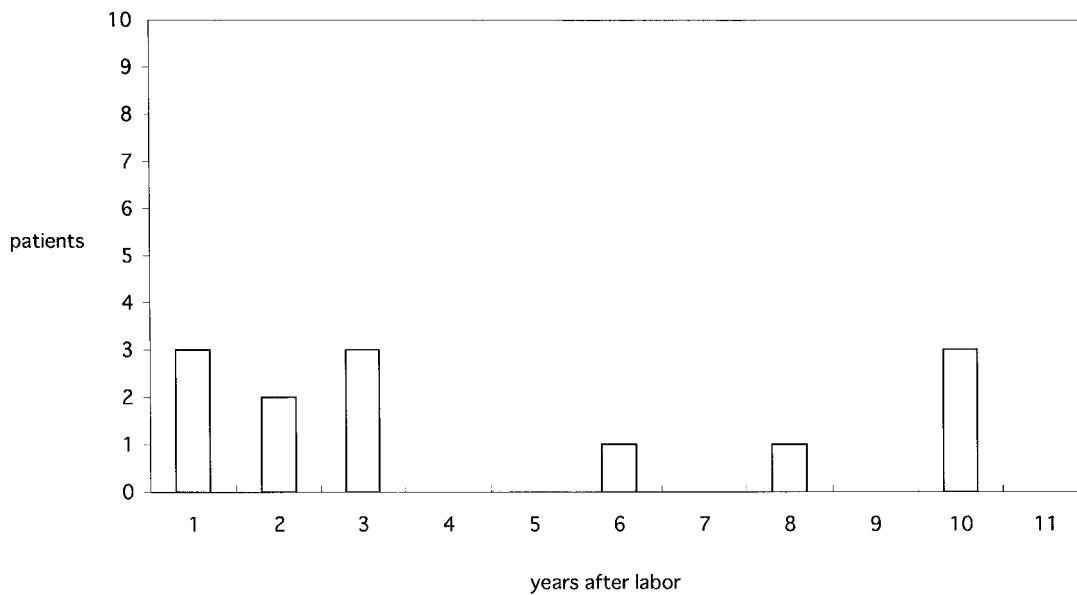


Fig. 3. Time to graft loss after delivery in renal transplanted women.

reported a live birth rate of 30% among 27 pregnancies [6]. In the most recent papers, in 1998, Okundaye *et al.* [6] described on infants survival rate of 40.2% in the 184 pregnancies in women who conceived after starting dialysis therapy and Bagon *et al.* [8] reported that the outcome was successful in 50% of pregnancies in haemodialysed patients. This current survey also confirmed that the rate of successful pregnancy in women on dialysis has improved in recent years [9]. The success rate rose remarkably from 9% in 1981 to 48.6% in 1996 in Japan, reflecting considerable progress in the management of pregnant women on dialysis.

Premature delivery is the most important problem for the children of women on dialysis and there is a higher rate of neonatal death. There are significant differences of mean gestational age and mean birth weight between surviving and non-surviving infants; those of the former are 33 weeks and 1726 g, while those of the latter are 26 weeks and only 700 g. Many

such extremely premature babies, even if they survive, have serious complications including cerebral palsy, brain atrophy and mental retardation.

It is still difficult to manage pregnancy in dialysis patients, who require very close cooperation between nephrologists and obstetric teams. For a successful outcome of such pregnancies, careful and scrupulous attention should be paid to dialysis strategy, problems of anaemia, fluid balance, blood pressure control, and maintenance of nutrition [10]. Guidelines aimed at optimizing foetal and maternal outcomes have been discussed in detail [10–13]. To prevent premature delivery, it may be most important to increase the frequency of haemodialysis.

By contrast with patients on dialysis, most pregnancies in transplanted women are successful, when graft function remains good and stable without proteinuria. The EDTA-ERA Registry reported that there have been 938 successful pregnancies in renal allograft

Table 3. Outcome of pregnancies in women on renal replacement therapy

	HD	Transplantation	P-value
Gestational age (mean)	31.9 ± 4.5 weeks	35.7 ± 3.2 weeks	<0.001
< 28 weeks	12 (26.7%)	3 (2.1%)	
28–32 weeks	6 (13.3%)	8 (5.6%)	
32–37 weeks	21 (46.7%)	74 (51.4%)	
≤ 37 weeks	6 (13.3%)	59 (40.9%)	
Birth weight	1543.5 ± 671.9 g	2360.1 ± 605.3 g	<0.001
< 1000 g	14 (31.1%)	5 (3.3%)	
1000–2500 g	28 (62.2%)	78 (51.3%)	
≤ 2500 g	3 (6.7%)	69 (45.4%)	
Neonatal death	9 (20%)	2 (1.0%)	<0.001

HD, haemodialysis.

recipients between 1965 and the end of 1991 [14]. In a survey of the world literature from 1961 to 1994, Davison [15] described that 93% of the gestations that continued beyond the 20th gestational week ended successfully, but the incidence of preterm delivery (50%) and of growth retardation (40%) with neonates of very low birth weight was still high. In this survey, 59.1% of pregnancies ended in preterm delivery and 54.6% of neonates were below 2500 g in birth weight, although the success rate of pregnancy was 98.7%.

According to observations collected by the National Transplant Pregnancy Registry in the United States [16], mean birth weight among live born infants of cyclosporin-treated mothers was 2407 g and among those of azathioprine-treated mothers was 2684 g, but this difference was not significant. However, there was a significant difference in the mean birth weight between 57 babies born to mothers on azathioprine ( $2567 \pm 491.1$ g) and 94 babies born to mothers on cyclosporin ( $2252 \pm 629.2$ g) in Japan.

It is a great concern whether pregnancy induces a risk of deterioration of graft function. This survey showed that deterioration of the graft function occurred in 20% of patients after labour and resulted in graft loss in almost 10% of patients after delivery. Recent retrospective case-control studies [3,17–19] to evaluate the long-term effects of pregnancy on graft function concluded that pregnancy did not have a deleterious long-term effect on graft survival, at least when the kidney graft is functioning well.

The survey revealed that there were few severe complications or major congenital anomalies in the children born to the transplanted women, although more than a half of pregnancies resulted in preterm delivery. Pregnancies in women with functioning kidney grafts obviously had favourable outcomes more frequently than did those of women on dialysis. There are significant differences in frequency of premature babies, birth weight, Apgar's scores and rate of neonatal death between pregnancies in women on dialysis and those of kidney transplant recipients (Table 3).

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