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Registry Report

Successful pregnancies in women on renal replacement therapy: Report from the EDTA Registry

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Abstract. This study reports the geographical incidence of successful pregnancies in women on renal replacement therapy (RRT) and related information on gestation and clinical status of newborns. The impact of successful pregnancy on graft function was assessed by means of a retrospective case-control study.

Since 1977 special questionnaires have been sent to each dialysis and transplant centre which reported babies born to mothers on RRT on the yearly centre questionnaire. After 10 years of data collection, a total of 490 pregnancies and 500 babies were available for analysis. A percentage of 88.4 of the babies were born to mothers with a functioning graft, 11.2% to mothers on chronic haemodialysis, and the remaining 0.4% to mothers on CAPD.

Almost 50% of all successful pregnancies were reported from the UK. The number of successful pregnancies increased steadily and in parallel with the increasing number of females of childbearing age with a functioning renal transplant. The majority of mothers delivered at age 24–32. For transplanted mothers delivery occurred most commonly during the 3rd and 4th year after successful transplantation.

In approximately 85% of cases the duration of pregnancy was shorter than the lower 10th percentile of normal. Birthweight was reduced in accordance with gestational age. Newborn mortality was 1.8%.

Fifty-three mothers with a successful pregnancy in 1984–1987 were computer matched with controls according to a number of criteria. The serum creatinine concentration recorded in coded form at the end of each year on the individual EDTA patient questionnaire was used to assess changes in graft function. In 94% of these cases the serum creatinine, recorded 0–11 months before delivery, did not exceed 160 μmol/l. Graft function deteriorated in 18% of

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mothers as compared to 24% of controls. Twenty-four to 36 months postpartum, changes of serum creatinine were similar in test cases and controls, suggesting that a successful pregnancy does not adversely affect graft function if this was stable and well preserved at the time of conception.

Key words: renal replacement therapy; pregnancy; newborns

Introduction

Successful renal transplantation is considered to be by far the best renal replacement therapy for patients in end-stage renal failure (ESRF). Transplantation activity and outcome continue to improve such that an increasing proportion of women in ESRF and of childbearing age now recover a normal reproductive function. For these women there is no doubt that successful pregnancy can be considered a sign of excellent rehabilitation from the original disease.

The reports on pregnancies in women after renal transplantation are quite numerous [1–17] but mainly describe the experience obtained in single centres and therefore relate to a relatively small number of cases. The main problems that have to be considered in transplanted women who wish to become pregnant are the potential risks to the fetus (survival, malformations) and the potential risks to the mother (survival, graft function). Given the relatively small number of successful pregnancies observed in each single centre, it is unlikely that statistically valid answers to these important questions can be derived from single-centre studies. In contrast, analysing the data collected on a large number of pregnancies over many years from all countries reporting to the EDTA Registry would be expected to yield answers regarding the general risk and other important aspects of pregnancy in mothers on RRT.

The purpose of this ongoing study is to evaluate the geographical distribution and the annual incidence of successful pregnancies in Europe and to collect information on the newborns and their survival at 1 month of life. It was also thought to be useful to evaluate the impact of pregnancy on graft function by means of a retrospective case-control study.

Subjects and methods

Demographic study

Since 1977 the EDTA Registry has paid special attention to those successful pregnancies which occurred in women on renal replacement therapy (RRT). Special questionnaires have been sent to each centre that reported one or more babies born to mothers on RRT on the yearly centre questionnaire. The first version of the special questionnaire is shown in Figure 1A. It was made simpler (Figure 1B) in 1984 by deleting the questions on breastfeeding, chromosome examination, drugs during pregnancy, body length,

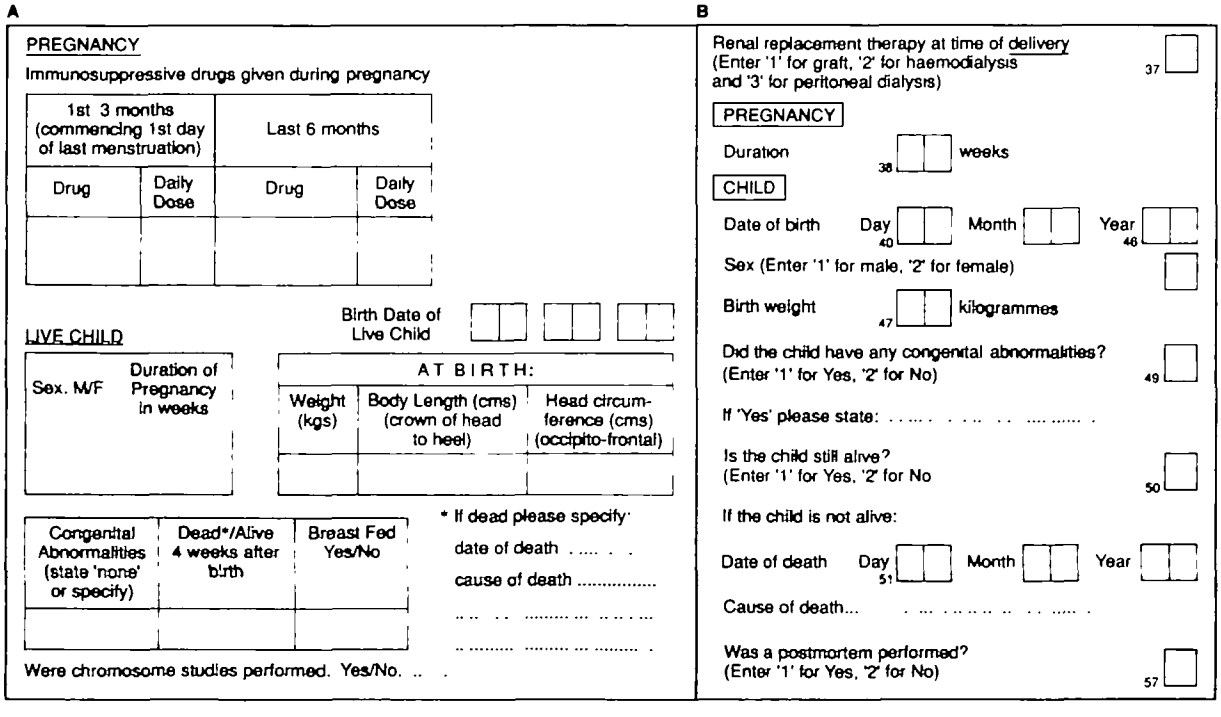

Fig. 1. The special questionnaire used 1977–83 (A) and since 1984 (B).

and head circumference. By the end of 1986, that is after 10 years, data on a total of 490 pregnancies and 500 babies were available for analysis (results on a smaller number of newborns were published earlier [18,19]).

Retrospective case-control study

Transplanted mothers with a successful pregnancy between November 1984 and January 1987 were identified on the EDTA Registry's patient files. Each of these test case mothers with a successful pregnancy was then matched by computer with a control case according to the following criteria: the test cases and controls had to come from the same country, to have received their first graft in the same year and from the same type of donor, and had to have identical codes for plasma creatinine concentration prior to the date of pregnancy. Control grafts had to be functioning at the date of the delivery of their respective test cases. The fully matched pairs (40 pairs) were female with a primary renal disease belonging to the same group of renal diseases. In a minority of controls (13 pairs) a difference in sex (6 pairs) and primary renal disease group (7 pairs) had to be accepted. However, the results obtained in the fully matched pairs were identical to those for pairs mismatched for sex and/or for primary renal disease group. For this reason all 53 case control pairs identified were included in the analyses shown below.

The concentration of plasma creatinine, as recorded in coded form at the end of each year for every patient with a functioning graft, was used to assess the impact of pregnancy on graft function.

Results

Among the 500 newborns reported to the EDTA Registry from 1977 to 1986 there were eight sets of twins and one set of triplets. The great majority of the newborns (88.4%) were born to mothers with a functioning graft; in only 11.2% and 0.4% of the cases the mothers were on long-term haemodialysis or CAPD respectively.

Demographic study

The country where most of the successful pregnancies occurred was the UK, which accounted for almost 50% of them; in countries like Italy or FRG only 0.5% or less of transplanted women of childbearing age had successful pregnancies. The number of successful pregnancies reported to the Registry each year steadily increased from 1977 to 1986, in parallel with the increasing number of renal transplants in Europe. This is shown in Figure 2 by the number of females with successful pregnancies as a proportion of all females with a functioning graft aged 17–40 in nine European countries. These proportions remained unchanged comparing the period 1977–1981 with 1982–1986. Two-thirds of the mothers were between 24 and 32 years old at the time of delivery (Figure 3); only a few successful pregnancies occurred in patients aged less than 21 and more than 40 years. Some 40% of deliveries took place during the 3rd and 4th year after transplantation (Figure 4), with a small percentage reported during the first year or as late as nine or more years after transplantation.

The length of gestation for babies born to women on RRT was much shorter than in the normal population (Figure 5); only 50% of babies had a

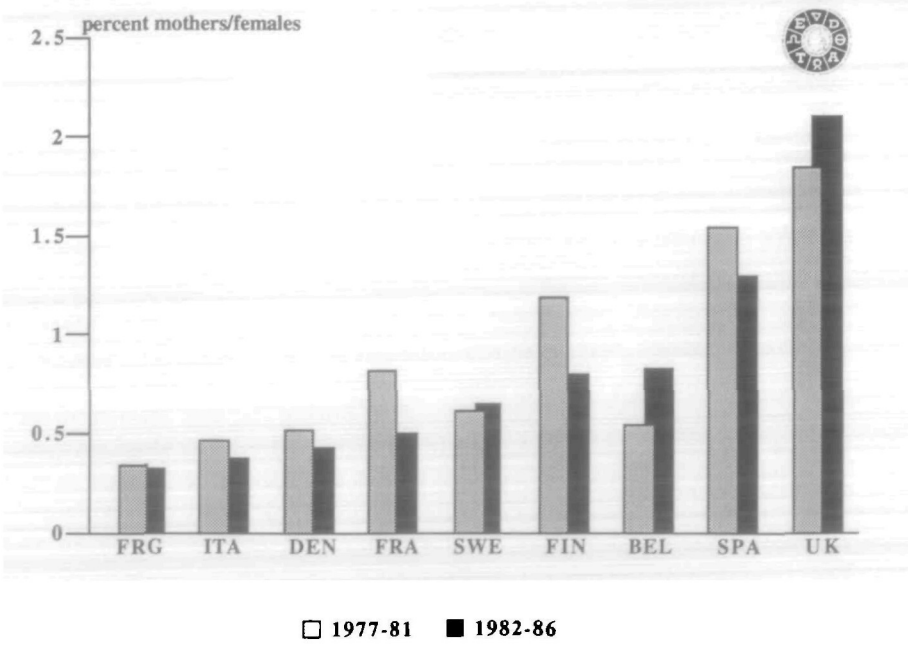

Fig. 2. Successful pregnancies in Europe in 1977–81 and 1982–86 as a proportion of all females with a functioning graft aged 17–40 at end of 1981 or 1986.

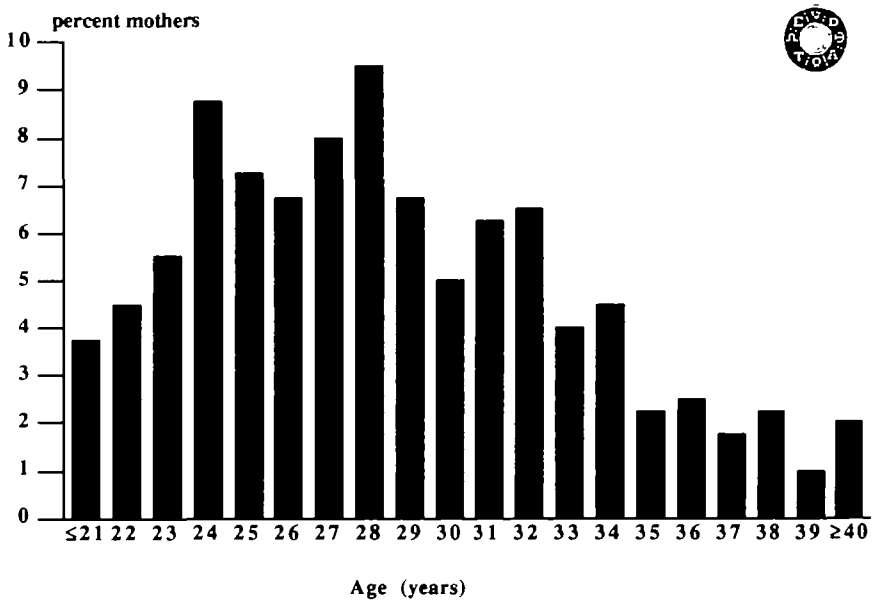

Fig. 3. Proportional distribution of women with successful pregnancies according to age at delivery.

Fig. 4. Time in years from graft to delivery shown as a proportion of transplanted women who had successful pregnancies Nearly half of the deliveries occurred between 2 and 5 years after grafting.

pregnancy of the normal 37 or more weeks duration compared with 90% in the general population. Figure 6 shows the distribution of birthweights of these same newborns compared with the distribution in the general population. It is worth noting that the majority of the babies born to mothers on dialysis were smaller than those born to mothers with a functioning renal transplant. The relationship between gestational age and birth weight was determined for babies born to mothers on RRT in 1983 (Figure 7); almost all fell between the 10th and 90th percentile for the normal population [18], suggesting that these newborns were small mainly because they were premature.

Nine newborns died during the first month of life (1.8%), and eight of them had a birth weight of less than 1.8 kg. The reported causes of death were acute respiratory distress syndrome (3), sudden unexplained death (2), 'malformation' (2), intracerebral haemorrhage (1), and prolapsed cord (1).

The detailed list of malformations reported on the questionnaires is given in Table 1; none of these malformations could be attributed to chromosomal causes, one case was monogenic (0.4%), and 11 cases

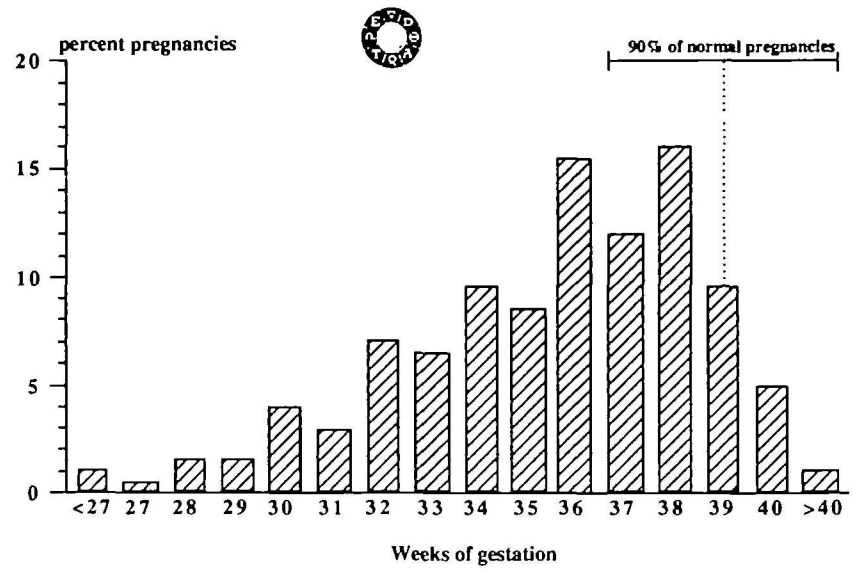

Fig. 5. Length of gestation in weeks shown as a proportion of women on renal replacement therapy who had successful pregnancies.

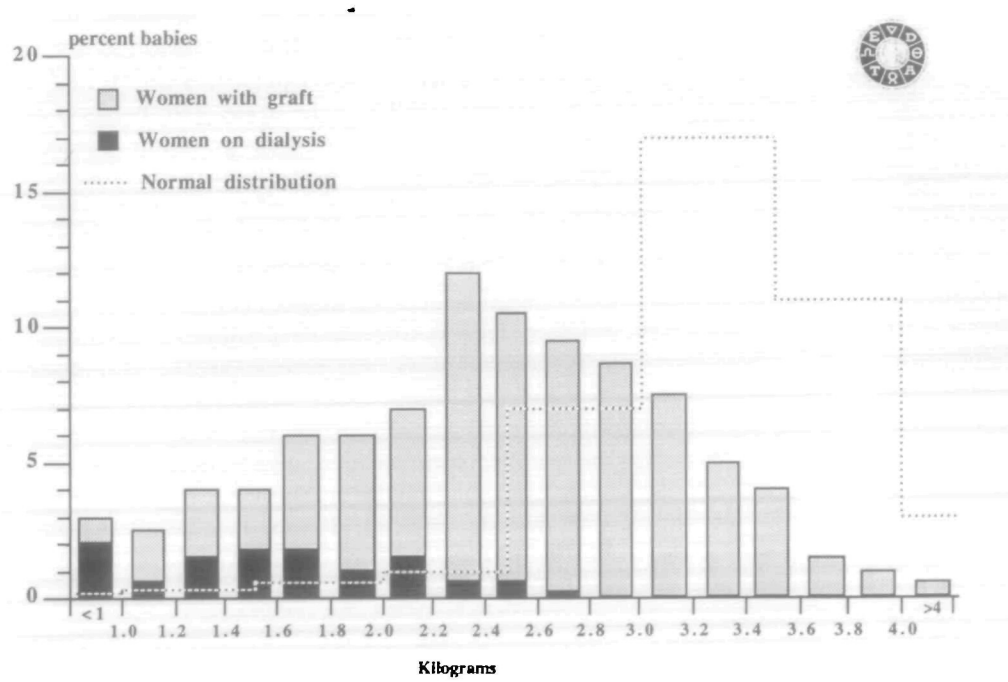

Fig. 6. Distribution of birth weights of 484 babies born to women on renal replacement therapy. Information on birth weight in the normal population is given for comparison.

appeared to be multifactorial (2.2%). In each category the number observed was within the limits expected for the newborn population.

Case-control study

From Table 2 it can be seen that 94% of all the transplanted women who had a successful pregnancy had a plasma creatinine concentration of 160 μmol/l or less (creatinine code 1 or 2) 0–11 months prior to pregnancy. Only three test cases, the remaining 6%, had a higher pre-pregnancy plasma creatinine recorded 1–4 months before the presumed time of conception. This clearly demonstrates that in this series, women who achieved a successful pregnancy usually had a normal or only slightly reduced graft function prior to gestation.

Figure 8 gives two examples of the relationship between the availability of plasma creatinine codes and gestation. Creatinine concentrations at the end of December of each year are recorded on the EDTA

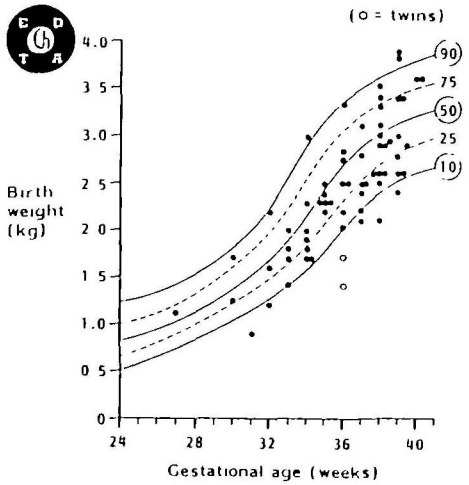

Fig. 7. Birth weights of babies born to mothers on renal replacement therapy in 1983 according to gestational age

Table 1. Congenital abnormalities reported to the Registry in 500 newborns

Congenital heart defect	5 (1 associated with oesophageal atresia)
Urinary tract malformation	3
Hypospadias	2
Gastrointestinal tract abnormalities (Hirschsprung, oesosphageal atresia, anal atresia, hernias)	4
CNS abnormalities (spina bifida, plagiocephaly, agenesia corporis callosi)	3
Cranial abnormalities (choanal atresia, cleft lip and palate)	2
Haemangioma frontalis	1
Medullary cystic disease	1
Bilateral clubfoot	1
Bilateral cataract	1
Pigeon chest and agenesis of thumb	1
Other	
Only 2 vessels in umbilical cord	1
'Congenital cytomegaly'	1
Phenytoin syndrome	1

In two cases the answer to the question on the presence of neonatal malformations was 'yes' but no specifications were given.

Table 2. Number and proportion of patients according to creatinine level before pregnancy. The time interval between the recorded serum creatinine and start of pregnancy ranged from 0 to 11 months

Code	μmol·l	*n*	%
1	<120	36	68
2	121–160	14	26
3	161–200	1	2
4	201–240	1	2
5	241–300		–
6	301–400	1	2
7	>400		-

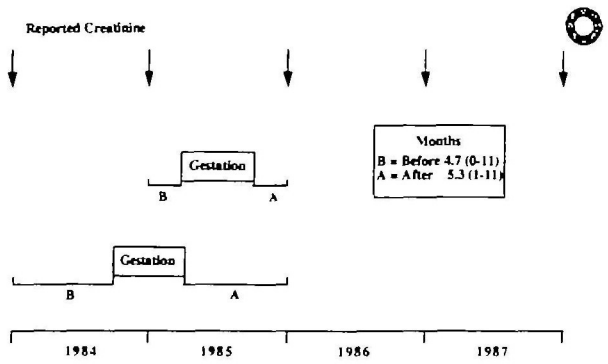

Fig. 8. Mean number (range) of months between the recorded serum creatinine and the beginning of pregnancy (B = before) and between the end of pregnancy and the next recorded serum creatinine (A = after).

patient questionnaire, as indicated by the arrows. Gestation could occur during a single calendar year (for example during 1985) and in this case the recorded creatinine used to evaluate renal function would be close in time both to the start of the pregnancy and to delivery. If the gestation took place during two calendar years (e.g. conception in 1984 and delivery in 1985) the time gap between the reported creatinine codes and gestation would be wider. Given these two possible situations for the 53 pairs included in the study, the average number of months between the nearest recorded creatinine and the beginning of pregnancy was 4.7 months (range 0–11 months) and 5.3 months (range 1–11 months) between delivery and the next available creatinine.

Figure 9 shows the results of the comparison between creatinine codes before and immediately following a successful pregnancy in test cases and in the matched controls for the same period. Creatinine codes indicated stable (or improved) graft function in both test and control cases in 67% of the pairs. In 9% of the pairs the test case became worse but the control did not; in 15% the control deteriorated

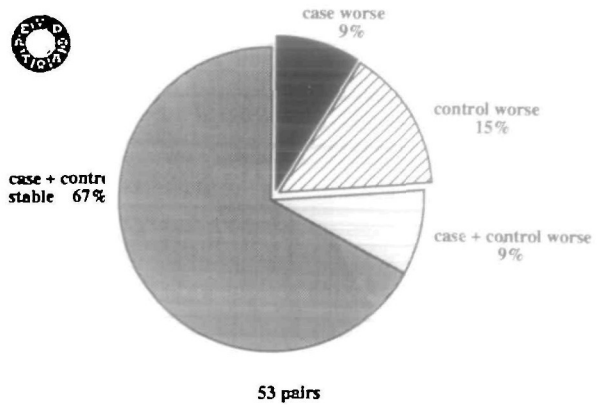

Fig. 9. Graft function according to creatinine level after successful pregnancy for cases and in controls as compared to graft function prior to pregnancy.

but the test case did not; in the remaining 9% renal function for both the test and the control cases deteriorated.

To see whether pregnancy produced an adverse effect on renal function during the later follow-up after delivery, the average value of the creatinine codes available for 42 pairs at 13–20 months and for 15 pairs at 25–35 months after delivery were calculated. The average value of the creatinine codes tended to increase (i.e. deteriorate) with time, both in the test and in control cases. However, test cases did not deteriorate more than the controls (Figure 10). There was a single mother who lost her graft 31 months after delivery, compared to five control cases with graft failure recorded at 7–31 months after date of delivery of the respective test cases.

Discussion

For a woman with a functioning graft to undergo a successful pregnancy is the best possible proof of 'rehabilitation' from ESRF. Many authors have reported the experience accumulated in their own centres [21,22] and have reviewed the literature [23–26] on this subject. Successful pregnancies in transplanted women have never been studied extensively in a uniform way on a European scale. The EDTA Registry has paid special attention to this important subject since the seventies and has collected information on one of the largest series ever analysed.

From the present study it is clear that the only problem for the newborns is prematurity and therefore a low birth weight, with the potential risks that this condition implies [24]. This study with its larger series also confirms that conventional immunosuppression (azathioprine and prednisone) does not result in more malformations evident at birth than seen in the normal population [19,20]. Preliminary data collected more recently by the EDTA Registry on 35 babies born to mothers on cyclosporin [27] do not suggest a higher incidence of malformations. Data on chromosome studies for a large number of such newborns are still missing. In this respect, chromosome studies reported to the first version of the EDTA questionnaire concerning 16 babies gave normal results in 14 and chromatid breaks, which are known to be reversible, in 2 [19,20]. Only 29 of 186 (16%) babies born between 1979 and 1982, reported on earlier, were breastfed by their mothers [20].

The mortality rate of 1.8% in these newborns may be an underestimation because it only refers to the first month of life and therefore does not include deaths after this period. It has to be recalled that the present study does not give any information on 'non-successful pregnancies', so that the total number of pregnancies initiated in this population is not known nor are the causes of miscarriage. Also, since information is not available, no conclusions can be drawn regarding potential late effects of immunosuppression in the mothers, which might emerge in their offspring after many months or years.

The present study clearly shows that successful pregnancies in women with a functioning transplant vary markedly in incidence among European countries. Moreover, the proportion of transplanted women of childbearing age who had a successful pregnancy did not increase from the mid-seventies to

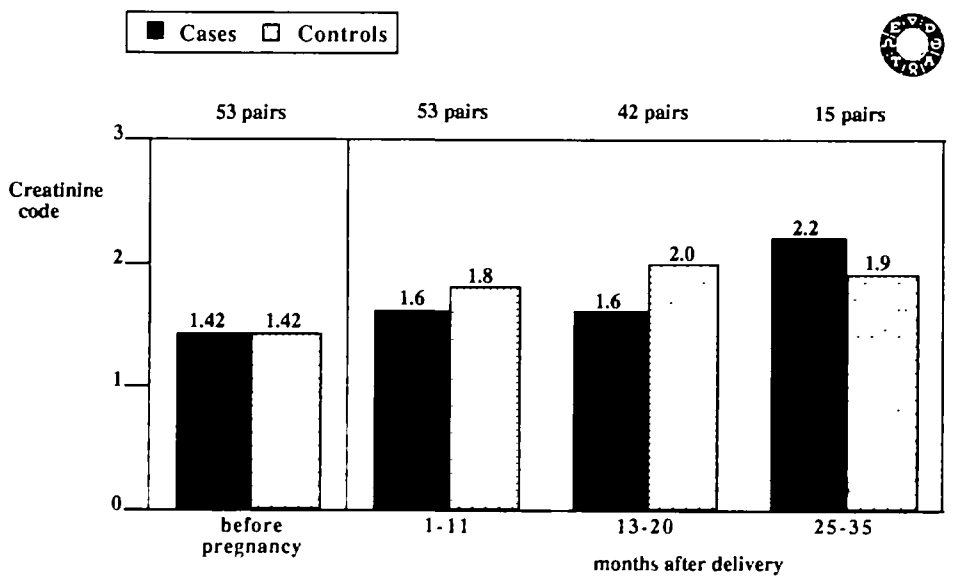

Fig. 10. Mean of creatinine codes before and after successful pregnancy and in controls with a functioning graft. Graft failure was recorded for one case 31 months after delivery and for five controls 7–31 months after their respective case's date of delivery

the mid-eighties. This clearly means that the attitude of the patients, of their families, and of the nephrologists regarding pregnancy in these subjects must differ from country to country. It is very likely that it is the medical attitude and belief which carry the greatest influence. No change over time in the proportion of transplanted mothers with successful pregnancies (Figure 2) could mean that it is always the same centres and doctors that have been in favour of a pregnancy, whilst the great majority probably have not supported, or have even discouraged, pregnancy in transplanted women. This majority of doctors, and consequently also their patients, still might consider pregnancy to be a risk for the graft function. It is also possible to imagine that in cases where transplantation had been awaited for a long time and had been experienced as a 'miracle' more than as a therapeutic procedure, the patient's expectations were fulfilled to the extent that she would not want to run any additional risk to her graft. This is all the more so as pregnancy has often been accused of adversely affecting graft function in a sizeable proportion of mothers [5,13,25].

In an earlier analysis of successful pregnancies, the Registry came to the conclusion that up to 17% of grafted mothers might suffer damage to their graft, with loss of graft function or even graft failure in association with the pregnancy [20]. However, other authors put forward the hypothesis that pregnancy could be considered to be relatively safe in women with a well-functioning graft [26,28]. Given the small number of pregnancies in transplanted women, the information available in the literature on the impact of successful pregnancy on graft function is limited and had never been studied by means of a comparison with a matched population in which there will always be found some individuals who lose renal function because of immunological or other causes.

For all of these reasons we decided to perform a retrospective case-control study. The results confirm that almost all women who had a successful pregnancy had a well-functioning graft beforehand. The number of mothers who suffered some decline in graft function, or who lost the graft, during a period of up to 3 years after delivery was certainly not greater than in the retrospectively matched control group which incurred a similar or greater loss of graft function without pregnancy. The results of the present analysis thus suggest that in general a successful pregnancy rarely if ever has a deleterious effect on graft function when this was normal or close to normal at the time of conception. It must be stressed that this study does not give any information on long-term evolution beyond 3 years after delivery, and on the impact of pregnancy in women with clearly abnormal graft function at the time of conception. The impact of 'non-successful pregnancies' on the graft function still remains to be elucidated. Earlier attempts by the EDTA Registry to collect data on abortions and stillbirths had to be abandoned. Such cases do not come to the attention of the Registry as the special pregnancy questionnaires have been sent exclusively to centres reporting 'live babies born to mothers on RRT'.

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