

Original Article

The children of dialysis: live-born babies from on-dialysis mothers in Italy—an epidemiological perspective comparing dialysis, kidney transplantation and the overall population

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ABSTRACT

Background. A successful pregnancy is an exceptional event on dialysis. Few data are available comparing pregnancy rates on dialysis, transplantation and the overall population. The aim of the study was to assess the incidence of live births from mothers on chronic dialysis compared with the overall population and with kidney transplant patients.

Methods. The setting of the study is in Italy between 2000–12.

Data on dialysis was acquired by phone inquiries that were carried out between June and September, 2013, involving all the public dialysis centres in Italy; the result was a 100% response rate. The data included was end-stage renal disease, type of dialysis, residual glomerular filtration rate, changes in dialysis and therapy, hospitalization; week of birth, birth weight, centile; and outcome of mother and child.

Information on transplantation was acquired by inquiry by the kidney and pregnancy study group who were contacted by phone or e-mail; the result was a 60% response rate. Data concerning prevalence of women in childbearing age (20–45) were obtained from the Italian Dialysis and Transplant Registries (2010–11 update).

Official site of the Italian Ministry of Health.

Results. During the study period, 23 women on dialysis (three on peritoneal dialysis) delivered live-born babies and one woman delivered twins (24 babies). Three babies died in the first weeks-months of life (including one twin); 19 of 21 singletons with available data were pre-term (33.3% <34 weeks); the prevalence of children <10th gestational age-adjusted centile was 33.3%. Birth weight and gestational age were lower in children from on-dialysis mothers as compared with 110 pregnancies following kidney graft, (weight: 1200 versus 2500 g; gestational age: 30 versus 36 weeks; $P < 0.001$). Incidence of live-born babies was inferred as 0.7–1.1 per 1000 female dialysis patients aged 20–45 and 5.5–8.3 per 1000 grafted patients in the same age range (Italian live-birth rates: 72.5 per 1000 women aged 20–45 years).

Conclusions. Having a baby while on dialysis is rare but not impossible, though early mortality remains high. There is a ‘scale of probability’ estimating that women on dialysis have a 10-fold lower probability of delivering a live-born baby than those who have undergone renal transplantation, who in turn have a 10-fold lower probability of delivering a live-born baby as compared with the overall population.

Keywords: counselling, dialysis, pregnancy, transplantation

'Oh figlio, figlio, figlio,
figlio amoroso giglio...'
'O son, O son of mine,
O lily-flower divine...'

Jacopone da Todi 'Donna de paradiso' XII Century.

INTRODUCTION

One of the first pregnancies on dialysis was reported by Confortini *et al.* [1] in the EDTA proceedings in 1971. Yet, over 40 years later, birth rates among mothers on dialysis have not been assessed in several countries including Italy. Epidemiological data are scant also because very few dialysis registries report data on pregnancies on dialysis, and efforts to quantify fertility are impaired by a relatively high rate of early fetal losses that may be easily missed, in particular in retrospective analyses [2–4].

Despite the paucity of data, a few large or systematic reviews highlight that over time the results of pregnancy in dialysis patients have greatly improved, with a gain in fetal survival of ~25% per decade, going from 23% in the European Dialysis and Transplant Association report in 1980, to ~50% in the 1998 report by Bagon *et al.*, to over 90% of live babies in the recent Canadian series of patients receiving high efficiency, long-nocturnal dialysis treatments [3, 5–9]. The growing number of positive reports on pregnancy in mothers on dialysis from all over the world demonstrates an increasing interest in this previously neglected issue [10–18].

Comparative data regarding pregnancy on dialysis and after transplantation are also scant [3, 19–21]. Hence, the statement that transplantation restores fertility and is the best way to allow a uraemic woman to conceive may have obscured the problem of pregnancy in dialysis [22–25]. However, although kidney transplantation is the 'number one therapy' for young patients, the lack of donor organs and the long waiting times, in particular for younger patients, may impair the possibility of receiving a kidney graft in time to begin a pregnancy.

Despite the rising interest in this issue, pre-conception counselling in clinical practice is rarely a part of the routine work-up for young women at the start of renal replacement therapy, and when it is carried out it seldom includes a discussion on the probabilities and problems encountered in a pregnancy on dialysis [4, 25–27].

Bearing these latter considerations in mind, the aim of the present study was to analyse the incidence of live births from mothers on dialysis in Italy in the new millennium (2000–12), as compared with the overall Italian population and to patients with a functioning kidney graft in the same period. This will be the basis for evidence-based counselling for young patients starting chronic dialysis.

Data from the dialysis and the transplant populations were inferred from the Italian Dialysis and Transplant Registry (RIDT) and from the National Transplant Coordination while we referred to the Italian Ministry of Health data for the overall Italian population (ISTAT) [28–32].

MATERIALS AND METHODS

Study design

The present study was planned in the context of a wider analysis of the long-term results of pregnancy in dialysis patients, with specific reference to the outcomes of children born to dialysis mothers.

The study was designed taking into account a previous inquiry by the Italian Study Group on Kidney and Pregnancy relative to the period between 1980 and 2007; the previously gathered data served as the quality control for the period between 2000 and 2007 (G. Daidone, unpublished data).

In the absence of Registry data on pregnancy in dialysis and after renal transplantation, the present analysis was based upon systematic phone interviews with all the public Dialysis Centres in Italy as well as with the most important private ones. This was followed by a banner on the Italian Society of Nephrology website and an email to all the patients and physicians affiliated with Associazione Nazionale Emodializzati Dialisi e Trapianto (ANED), the Italian association of dialysis and transplant patients.

The analysis was cooperative and was carried out by the Italian Study Group on Kidney and Pregnancy in cooperation with the Italian Registry of Dialysis and Transplantation, and with the support and cooperation of ANED. The list of the Italian Centres was made available by ANED.

The choice of basing the interviews on the public dialysis centres was motivated by the fact that the large dialysis centres connected with other hospital structures (i.e. gynaecology) are public in Italy, as well as by the assumption that patients who are treated at smaller dialysis units would be referred to larger, public centres for pregnancy follow-up and delivery. Since the care of dialysis patients is in any case a team effort in Italy, the inquiry was based upon calls to the centres; the individual nephrologists, members of the Italian Society of Nephrology were however also contacted via the society banners and newsletters. All of the 393 public dialysis centres were contacted by phone and all of them replied. Furthermore, a capillary inquiry by members of the study group was dedicated to the regions in which private dialysis is more widespread (Sicily: 123 private centres, Lazio 73, Campania 137 and Puglia 42).

The coordinator of the Dialysis Registry also made sure that all the information was shared among the regional registries.

Since the study period was relatively long (2000–12), miscarriages (before the 24th week) were not included in order to reduce the reporting bias. Furthermore, although data on miscarriages after the 24th gestational week were collected, we decided to focus on the more robust data concerning live-born babies, considering them as being less subject to report biases.

To avoid including patients with acute diseases, only patients who were already on dialysis, or those who started chronic dialysis during the first 3 months of pregnancy were included.

Sources of data: live-birth from mothers on dialysis

After having identified the patients, the following data were collected: name (code), centre, date of birth, date of renal

replacement therapy (RRT) start, maternal age at conception, type of disease, complications during pregnancy and, in particular with respect to hypertension control, residual function at conception, drugs, additional care, dialysis schedule, main modifications of the dialysis schedule in pregnancy, gestational age, birth weight, indication to delivery, mode of delivery, other maternal complications (short and long term), stillbirth/neonatal death (excluding miscarriages and termination before the 24th week of pregnancy), small for gestational age babies (SGAs), Apgar scores, admission to an intensive-care unit, other neonatal complications (short and long term), follow-up of the mother (grafted, on dialysis) and of the child; in the case of death, date and cause of death. SGAs were defined both as below the 5th centile and as below the 10th centile, adjusted for gestational age, according to Parazzini and to InES charts [33, 34].

Demographic and clinical data were supplied by the caregivers and checked during the interviews with the patients and/or families, which were carried out at each participating centre by the same team. In particular, since the definition of pre-eclampsia is not universally agreed upon for dialysis patients (impossibility to refer to proteinuria), patients who developed hypertension in late pregnancy were defined as 'severe hypertension'. Since it was not possible to establish the difference between pre-mature rupture of membranes (PROM) and spontaneous labour, in particular in early pre-term babies, we recorded the diagnoses as reported in the clinical charts.

Sources of data: live birth after transplantation

Data were supplied by the Study Group on Kidney and Pregnancy that had performed the survey: the analysis was targeted at assessing pregnancy rates as of the opening of each of the transplant centres (mainly in the early 80s). To do so, the transplant centres (all public) were contacted by phone and e-mail by the study group coordinators and were asked to provide information concerning the pregnancies that were reported in kidney transplant patients. Replies were obtained from 15 of 26 Italian transplant centres. Considering that most patients are grafted at their regional centres, the survey covers ~60% of the Italian transplanted population. Hence, the 110 reported pregnancies in 60% of the Italian population led to an inference of 183 pregnancies occurring throughout the whole period in the overall Italian kidney graft population.

The following information was selected from the larger database of the Study Group: live births and deliveries after 1 January 2000. The following data were collected: code, centre, date of birth, date of RRT start, maternal age at conception, type of disease, gestational age, birth weight, pre-term delivery, small for gestational age, follow-up of the mother (grafted, on dialysis) and of the child; in the case of death, date and cause of death. Data on miscarriages were not used for the present analysis, which were limited to live-birth rates.

A subsequent phone survey was carried out to confirm the long-term outcomes of all babies born either extremely pre-term (before the 28th gestational week), or SGA of <5th centile. None of the babies was reported as having died in the first 6 months of life.

Sources of data and statistical analysis

The overall Italian population encompasses ~60 million inhabitants. The data were obtained from the ISTAT registries, as available online on the Italian Ministry website [30]. Since the overall Italian population and the dialysis populations are remarkably different as per age stratification (20% of subjects aged over 65 years versus 60% in the dialysis population), live-birth rates were calculated with respect to the female population aged 20–45. Live-birth rates in the study period were 9.06/1000 inhabitants, corresponding to 72/1000 women aged 20–45 (simplified inference: males: females 50%, age 20–45: 25% of the Italian population) [30, 31].

Dialysis and transplantation: as the coverage of the RIDT is not complete, data were obtained from various sources and projections were integrated and compared. The French Registry of Dialysis and Transplantation was also considered for reference and control as its coverage is complete and the incidence and prevalence data of RRT are comparable for the two countries [30–32].

With regard to Italy, taking into account the availability of pooled data alone, the following assumptions were made: RRT patients: males 60% and females 40%; prevalence on dialysis of the 20–45 age group: 9.4% [31, 32] and prevalence after graft of the 20–45 age group: 50%. Furthermore, the inference took into account the stability of the 20–45 cohort on dialysis and after transplantation (increases limited to older patients). On the basis of the overall available data, we referred to a range: 42 000–50 000 patients on dialysis [31, 33] and prevalence of kidney transplant patients: 17 226 (2005) and 25 000 (2012) [31–34].

Descriptive analysis was performed as appropriate (mean and standard deviation for parametric data and median and range for non-parametric data). Paired *t*-test, χ^2 test, Fisher's test, Kruskal–Wallis test, Mann–Whitney *U*-test, analysis of variance and *t*-test with Bonferroni correction were used for comparisons between patients and controls and among groups. Significance was set at <0.05. Statistical evaluation was performed using SPSS vers. 18.0 for Windows (SPSS, Chicago, IL, USA).

Ethical issues

The observational study protocol was approved by the Ethics Committee of the University of Torino (Azienda Sanitaria Ospedaliera san Luigi; delibera del Direttore Generale n.364 17 June 2013). All the participants signed an informed consent form for the anonymous treatment of data regarding pregnancy and delivery, and for the anonymous treatment of data regarding the child. When the mother was unavailable, we asked the closest family member for consent and participation.

RESULTS

Summary data: the mothers

The present inquiry allowed us to retrieve data on 23 pregnancies with 24 live-born babies (one was a twin pregnancy) between 2000 and 2012 (Table 1). Only one patient (Case 23)

Table 1. Main demographic and dialysis data: mothers on dialysis with live-born babies, according to date of delivery (Italy: 2000–12)

Case	Year of delivery	Start of RRT (year)	Age at RRT start (years)	Age at delivery	ESRD	Diuresis at start of pregnancy (mL)	Type of dialysis	Schedule at start hours x sessions	Max schedule hours x sessions	Outcome at October 2013
1	2000	1999	29	30	Unknown	800	HD	4 × 3	4 × 5	Grafted
2	2001	1998	30	33	IgA	1500	HD	4 × 3	5 × 5	Grafted
3 ^a	2001	2001	22	22	Dysplasia	1500	HD	3 × 2	4 × 3	Dialysis
4	2002	1990	28	40	GNM	Absent	HD	4 × 3	4 × 6	Grafted
5	2003	1995	34	42	Chronic PN	Absent	HD	4 × 2	4 × 6	Dialysis
6 ^a	2003	2003	30	30	IgA	1500	PD	–	Increase	Grafted
7	2003	1986	19	36	SLE	Absent	HD	4 × 3	4 × 6	Died: intestinal infarction (2013)
8 (twins)	2004	1997	31	38	Interstitial	Absent	AFB	4 × 3	4 × 6	Grafted
9	2005	1999	33	31	SLE	800	HD	4 × 3	4 × 6	Grafted
10	2005	1997	19	27	GNM	Absent	HD	4 × 3	4 × 5	Grafted
11	2006	1998	26	34	IgA	Absent	HD	4 × 3	4 × 6	Died: cerebral haemorrhage (2007)
12	2006	2005	28	29	Chronic PN	1000	HD	4 × 3	4 × 6	Dialysis
13 ^a	2007	2007	38	38	Unknown	2000	PD	–	No change	Dialysis
14	2008	2006	25	27	IgA	1500	PD	–	Increase	Grafted
15	2008	2007	29	30	Unknown	800	HD	4 × 3	4 × 6	Grafted
16	2008	2002	24	30	Chronic PN	Absent	HD	4 × 3	6 × 7	Dialysis
17	2009	2004	18	23	Unknown	Absent	HD	4 × 3	4 × 6	Dialysis
18	2009	2008	33	34	vasculitis	1200	HD	4 × 3	4 × 6	Grafted
19	2009	1994	21	36	Reflux	Absent	HD	4 × 3	4 × 6	Dialysis
20	2009	2007	28	30	vasculitis	Absent	HD	4 × 3	4 × 5	Grafted
21 ^a	2010	2010	27	27	Unknown	800	HD	3 × 1	4 × 6	Grafted
22	2011	2003	29	37	IgA	Absent	HD	start	4 × 6	Dialysis
23	2012	/	/	38	Unknown	Unknown	HDF	4 × 3	4 × 5	/

RRT, renal replacement therapy; ESRD, end-stage renal disease; IgA, IgA nephropathy; GNM, membranous nephropathy; SLE, systemic lupus erythematosus; PN, pyelonephritis; Reflux, reflux nephropathy; HD, bicarbonate haemodialysis; PD, peritoneal dialysis; AFB, acetate free biofiltration; HDF, haemodiafiltration; /, no answer.

^aMothers who started dialysis in pregnancy.

requested not to be mentioned and to avoid reporting data that could identify her in our study (Tables 1 and 2).

The causes of end-stage renal disease (ESRD) reflect the most frequently encountered ones among young patients. Of note, two patients were affected by systemic lupus erythematosus and two by vasculitis.

Residual diuresis, as recorded in the clinical charts, was absent in about half of the patients, thus reflecting the differences in dialysis vintage in this population (Table 1). Four patients started dialysis at the beginning of pregnancy and in two of them pregnancy was unexpectedly discovered after dialysis start (Table 1). No significant difference was found in the incidence of small for gestational age (SGA: <10th centile) babies in patients with or without residual diuresis. Considering singletons for whom data were available, we found four SGA babies in the subset of 10 patients with residual renal function and 3 of 11 without residual diuresis (*P*: ns). The week of delivery and the presence of hypertension were likewise not associated with SGA; hypertension and residual diuresis were not mutually associated (Tables 1 and 2).

Three patients were on peritoneal dialysis (PD) and 20 were on bicarbonate dialysis or haemodiafiltration. The most common change during pregnancy was an increase in dialysis frequency, up to a maximum of 6 h, 7 days a week (Case 16); the most common schedule was 4 h six times per week.

Interestingly, hypertension was not the rule in this population during pregnancy, as about half of the patients were normotensive at the start of pregnancy (10 of 22 with available data), and 8 of 22 were normotensive throughout pregnancy (excluding the last preeclampsia-like phases, occurring in 2 of 8); hypertension developed in five cases, while blood pressure normalized in three patients and control improved in one (Table 2).

Two mothers died over follow-up: the causes of death were intestinal infarction (10 years after delivery) and cerebral haemorrhage (1 year after delivery). Gross mortality (1.5 per 100 years of observation) is in keeping with the overall data of the young RRT population.

Summary data: children and delivery

The present survey considers only live-born babies; three babies died over the first days months of life. There were two singletons and one twin. All three babies were males, all were 'early' pre-term (28–30 weeks), none was small for gestational age; two third of the mothers were hypertensive and kidney disease had not been diagnosed in two there was interstitial nephropathy in one.

Pre-mature birth was almost the rule (19/21 singletons with available data), and the prevalence of 'early pre-term' (i.e. before the 34th completed week of pregnancy) was very high (7/21). Three babies, who were born before the 28th gestational week,

Table 2. Main materno-fetal outcomes: mothers on dialysis with live-born babies, according to date of delivery (Italy: 2000–12)

Case	Ht pre	Ht Pregn ^a	Hospitalization (besides delivery)	Hosp. at delivery	Week of delivery	Reason for delivery	Delivery	Sex	Weight (g)	Centile InES	NICU days	Problems (beside prematurity)
1	N	N	–	10	28	Spont. labour	CS	F	1200	79	20	–
2	N	Y	–	na	33	Spont. labour	CS	M	2250	77	7	–
3	N	Y	Abdominal pain	4	36	PROM	CS	F	1000	1 SGA	30	RD
4	N	N	–	7	32	PROM	V	M	1100	2 SGA	na	–
5	Y	Better	Polydramnios liver enzyme increase	7	26	PROM	CS	M	1073	93	30	Arm dysplasia
6	Y	Y	–	10	33	Severe Ht	CS	F	1600	20	45	–
7	N	N	Last 40 days	na	28	Severe Ht	CS	M	1150	65	75	–
8 (twins)	Y	Y	Amniocentesis	28	29	Severe Ht IUGR	CS	M F	1065 680	M: 24, F: 2 SGA	M: died at 3 days; F: 120	RD
9	Y	Y	Pancreatitis	5	34	Spont. labour	CS	F	1450	4 SGA	20	RD
10	N	Y	Bleeding (25 w)	21	30	PROM	CS	M	1200	27	na	–
11	Y	N	Not clear (20–33 w)	9	37	Spont. labour	CS	F	2010	2 SGA	No	–
12	N	N	Hyperkalaemia	7	36	Spont. labour	CS	M	2230	10	No	–
13	N	N	Polydramnios, peritonitis	4	35	PROM	V	F	1880	9 SGA	No	–
14	Y	Y	–	9	26	Spont. labour	CS	M	590	9 SGA	Died after 120 days	Pneumonia; abdominal hernia
15	N	N	–	4	30	Severe Ht	CS	F	1400	59	15	Patent ductus
16	Y	Y	–	na	30	Fetal reasons	CS	M	1070	14	15	RD
17	Y	Y	–	7	26	Spont labour	CS	M	840	54	90	RD; patent ductus, retinitis, abdominal hernia
18	Y	Y	–	10	34	Alteration in fetal tracing	CS	F	2060	42	No	–
19	Y	N	–	5	37	Spont. labour	CS	F	2000	44	No	–
20	Y	Y	Contractions, fistula thrombosis	na	32	PROM	CS	M	1200	5 SGA	Died after 2 weeks	–
21	N	Y	Hypertension	28	28	Severe Ht	CS	F	900	27	60	–
22	Y	N	Amniocentesis	7	35	HELLP	CS	M	2140	19	No	–
23	/	/	/	/	/	/	/	/	/	/	/	Alive

Y, yes; N, no; M, male; F, female; Ht, hypertension; na, not available; pre, before pregnancy; pregn, pregnancy; NICU, neonatal intensive-care unit; Spont labour, spontaneous labour; PROM, pre-mature rupture of membranes; CS, caesarean section; V, vaginal delivery; SGA, small for gestational age baby; RD, respiratory distress; HELLP, HELLp syndrome; /, no answer. ^aExcluding the last week of pregnancy (pre-eclampsia-like syndrome).

were considered ‘extremely pre-term’; all survived without evidence of long-term clinical problems. One-third of the singleton children with available data were small for gestational age: <10th centile 7/21; <5th 4/21.

No major malformations were reported in any of the children who survived.

Comparison of maternal-fetal outcomes: dialysis versus transplantation

A comparison of the data reported in the same period between children born to mothers with a kidney graft and those born to mothers on dialysis underlines an overall significantly higher incidence of prematurity in children from on-dialysis mothers (90.48 versus 52.34%), while the incidence of early pre-term babies, albeit higher on dialysis, does not reach statistical significance (Table 3). Consequently, a significantly higher birth weight is reported for children born to grafted mothers (median 2500 versus 1200 g). The incidence of SGA (SGA<10th centile) is almost twice as high for women on dialysis (33.33 versus 16.67%) while the incidence of SGA <fifth centile does not reach statistical significance (Table 3).

None of the reported children born to grafted mothers died over follow-up. Conversely, three babies born to on-dialysis mothers died (two singletons one twin); the difference is statistically significant ($P = 0.0267$).

Live-born rates with respect to the overall dialysis population and to the grafted population

Considering the Italian live-birth rates (2011 ISTAT data: overall population birth rates: 9.02 live births per 1000 population), and taking into account the composition of the general population versus the dialysis population, we calculated a live-birth rate of 72.5 per 1000 subjects in the general female population aged 20–45 years (Table 4).

As for dialysis, the 24 live-born children were related to the female dialysis population in the same age group; the prevalent cases were inferred from various sources and the highest and lowest calculations were employed; this led to an incidence of 0.7–1.1 live-born babies per 1000 women on dialysis, aged 20–45 years.

The corresponding figures in transplantation were indicatively 5–10 times higher (5.5–8.3 per 1000 women in the age

Table 3. Main pregnancy outcomes: comparison between children born to mothers on dialysis and after transplantation (singletons only)

	Week of gestation (median, range)	Early pre-term % (<34 weeks)	All pre-term % (<37 weeks)	Weight (median, range)	SGA (<5 centile)	SGA (<10 centile)	Perinatal death
Dialysis patients	30 (26–37)	7/21 (33.33%)	19/21 (90.48%)	1200 (590–2250)	4/21 (19.05%)	7/21 (33.33%)	2/22 (9.09%)
Kidney transplant patients	36 (25–40)	27/107 (25.23%)	56/107 (52.34%)	2500 (820–4000)	9/101 (8.91%)	17/101 (16.67%)	0/110
P dialysis versus graft	<0.001	0.4307	0.0012	<0.001	0.2355	0.0030	0.0267

SGA, small for gestational age baby.

Table 4. Live-born rates in on dialysis and after kidney transplantation, as compared with the overall Italian population

	Live births in the overall dialysis and transplant populations	Patient-years of observation age 20–45 females	Live-birth rate age 20–45 per 1000 subjects	Baseline employed data and assumptions followed
Dialysis patients	24	22 000–35 000	0.7–1.1	24 Births observed the whole population. Inference for M:F = 60:40. Age 20–45 = 10% of the overall population. Prevalent dialysis patients: range of the estimation 36 000–50 000. Stable prevalence in 2000–12 in the age group 20–45.
Kidney transplant patients	183	22 000–33 000	5.5–8.3	110 Live births observed in mothers with a kidney graft, with data available from the transplant centres covering ~60% of the Italian population. Inference for M:F = 60:40. Age 20–45 = 30% of the overall population. Prevalent grafted patients: range of the estimation: 18 000–21 000. Stable prevalence in 2000–12 in the age group 20–45.
Italian population	–	–	72.5	Italy ~60 million inhabitants stable birth rates in the period 2000–12. Overall population live-birth rate: 9.02; inference for M:F = 50:50; age 20–45 = 25% of the overall population; due to the very low birth rate in the ages 15–19, the rates were inferred as due only to the 20–45 years age group, in females only.

range 20–45 years). Hence, the probability of delivering a live-born baby, compared with the overall Italian population, may be rounded to 1:10 for women with a functioning kidney graft and 1:100 for women on chronic dialysis (Table 4).

DISCUSSION

Pregnancy is a great challenge for women on dialysis and for their caregivers

While for several decades kidney transplantation was considered not only the best, but also possibly the only way to restore fertility in uraemic women, an increase in interest towards pregnancy in dialysis has been recorded in the new millennium [2–4, 8, 9, 11–18, 35–42].

Hence, the present nationwide Italian survey was undertaken to assess the incidence and the main clinical characteristics of live-born babies from women on dialysis, also with respect to transplanted patients and to the overall population.

From a clinical point of view, the main results may be summarized as reflecting the unpredictability of this rare event. In fact, the epidemiological and clinical data are scattered: pregnancies were recorded all over the country, in small as well as in large centres; no referral centre was identified since three of

the centres followed only two pregnancies each during the study period. This may be seen as an opportunity to reflect on the importance of highly specialized units like the ones that are present in other countries [9, 11, 12, 14, 15], but it also demonstrates that by providing strict clinical surveillance and a strong patient–physician relationship, virtually all dialysis centres could lead a pregnant patient to a successful outcome.

The clinical features are likewise non-homogeneous, and a successful outcome (a surviving live-born baby) was also reported in patients with a priori negative outcome predictors, i.e. without residual diuresis, with ‘difficult’ diseases, such as systemic lupus erythematosus (SLE) and vasculitis, and with long RRT vintage (over 10 years in two patients). While precise, retrospective quantification of the residual function may be difficult, the presence of the residual diuresis that was reported was highly consistent with dialysis vintage and may be considered reliable. Since only four patients started chronic dialysis at the beginning of pregnancy (and pregnancy was actually a surprise for two of them), we cannot compare our data with registry surveys which suggest that the start of dialysis in pregnancy is associated with better outcomes [2, 43].

A potential point of interest regards hypertension: in fact, only about half of the patients were hypertensive at the start of pregnancy and, while hypertension developed in five previously

normotensive subjects, three hypertensive women became normotensive in pregnancy and blood pressure control improved in one (Table 2). Since dialysis was intensified in all cases, this may be seen as further indirect support of the role played by daily dialysis in hypertension control [44].

Our results are in line with a recent report comparing pregnancies on long-nocturnal dialysis in Canada and on shorter dialysis in the USA. Even if the different study design prevents a precise comparison, the median gestational week in our series (30 weeks) was about halfway in between the almost physiological median gestational age in Canada, and the very low one in the USA (27 weeks), and is also in keeping with an intermediate dialysis time (equal or >24h per week in most of our cases) [45].

In our series, neonatal death occurred in two singletons and in one twin but it was not associated with SGA or with maternal disease; all babies who died were 'early pre-term', none was SGA.

Maternal survival after delivery was apparently not affected by pregnancy; two deaths were recorded, with a gross mortality of 1.5 per 100 patient-years of observation. Once more, our results may both be seen as a mere effect of the rarity of the event, but may also underline that there is no reason for limiting a priori this possibility to a dialysis patient (Tables 1 and 2).

From an epidemiological point of view, our study is the first one in Italy and likely the first one in Europe to report the incidence of live-born babies with respect to the overall population and to women with a kidney graft, thus allowing us to define a sort of probability scale showing an almost 10-fold difference between dialysis and transplantation and between transplantation and the overall population (Table 4). In other words, the odds of giving birth to a live baby were found to be reduced by ~1:70–1:100 in a dialysis patient as compared with the overall population and by ~1:5–1:10 with respect to the kidney graft population. Although the results for this latter group show a lower incidence of prematurity and higher birth weight as compared with dialysis patients, they are still far from the standards of the overall population (Tables 3 and 4). Interestingly, the 1:10 ratio between dialysis and transplant patients, and the stepwise decrease of live-born rates from the general population to transplantation and dialysis is in line with data recently reported by the DATA Registry that collected data on 30 live-born babies in mothers on dialysis between 1966 and 2008 [2].

Our study has several limits, most of which are shared by retrospective surveys: despite all our efforts, we cannot be formally sure of having retrieved data regarding all the actual patients. However, the multi-step data collection, that started with phone calls to all of the >300 public dialysis centres and involved via the local members of the study group all the major private dialysis centres, provided a solid database. The involvement of the co-ordinator of the Italian registry of dialysis and transplantation allowed the request to be made to all the Italian regions, and above all, the most important Italian Patients' Association (ANED) allowed us to cross-check the data, which we now consider to be complete.

Furthermore, the data discussed herein are limited to live births and cannot answer one of the most crucial questions

asked by a woman who wants a baby, i.e. what are her chances of getting pregnant and of carrying the pregnancy to a viable phase for delivery. While an indirect answer may come from an analysis of the literature data, which suggest that up to 30–40% of pregnancies on dialysis end in an early miscarriage and that a further 10–30% are lost in the last phases, only prospectively designed studies may identify early losses or voluntary pregnancy termination [2–4, 17–21, 37–41]. Hence, the interest in this rare, crucial event supports the systematic collection of pregnancy data in dialysis registries.

A further limit of our study is the multiple inferences that were needed for the comparisons; the lack of complete data from the RIDT forced us to derive data from different sources.

Within these limits, one of the strengths of the study is that it provides a recent, nationwide European comparison of live-birth rates in women treated by dialysis and transplantation, and it confirms that the previous data indicating that giving birth do not impair survival in ESRD patients apply not only to kidney transplant patients but also to on-dialysis patients.

CONCLUSIONS

Having a baby while on dialysis is a rare event, but it is possible. A positive outcome may be observed even in women with systemic diseases such as vasculitis or systemic lupus erythematosus or in those without residual diuresis and with long RRT follow-up.

Despite these encouraging observations, mortality remains high (2/22 singletons), and prematurity and low birth weight are the norm. In spite of increases in dialysis frequency and/or duration, the results are still less favourable than after kidney graft.

There is a 'scale of probability' with about a 10-fold decrease in probability of delivering a live-born baby from the overall population to kidney transplantation and from kidney transplantation to dialysis. Further qualitative and quantitative studies are needed to support counselling to families and physicians on this topic and especially as far as the psychosocial development and the long-term outcomes of mothers and children are concerned.

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CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract format. None of the authors has any conflict of interest.

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