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Original Articles

Children of a lesser god or miracles? An emotional and behavioural profile of children born to mothers on dialysis in Italy: a multicentre nationwide study 2000–12

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ABSTRACT

Background. Pregnancy on dialysis is increasingly being reported. This study evaluates the behavioural profile of the children of mothers on dialysis and the parental stress their mothers undergo when compared with a group of mothers affected by a different chronic disease (microcythaemia) and a group of healthy control mothers.

Methods. Between 2000 and 2012, 23 on-dialysis mothers gave birth to 24 live-born children in Italy (23 pregnancies, 1 twin pregnancy, one of the twins deceased soon after delivery); of these, 16 mothers and 1 father (whose wife died before the inquiry) were included in the study (1 mother had died and the father was unavailable; 2 were not asked to participate because their children had died and 3 were unavailable; children: median age: 8.5, min–max: 2–13 years). Twenty-three mothers affected by transfusion-dependent microcythaemia or drepanocytosis (31 pregnancies, 32 children) and 35 healthy mothers (35 pregnancies, 35 children; median age of the children: 7, min–max: 1–13 years) were recruited as controls. All filled in

the validated questionnaires: ‘Child Behaviour Checklist’ (CBCL) and the ‘Parental Stress Index-Short Form’ (PSI-SF).

Results. The results of the CBCL questionnaire were similar for mothers on dialysis and healthy controls except for pervasive developmental problems, which were significantly higher in the dialysis group, while microcythaemia mothers reported higher emotional and behavioural problems in their children in 8 CBCL sub-scales. Two/16 children in the dialysis and 3/32 in the microcythaemia group had pathological profiles, as assessed by T-scores (p: ns). PSI-SF indicated a normal degree of parental stress in microcythaemia subjects and healthy controls, while mothers on dialysis declared significantly lower stress, suggesting a defensive response in order to minimize problems, stress or negativity in their relationship with their child.

Conclusions. According to the present analysis, the emotional and behavioural outcome is normal in most of the children from on-dialysis mothers. A ‘positive defence’ in the dialysis mothers should be kept in mind when tailoring psychological support for this medical miracle.

Keywords: depression, dialysis, ESRD, pregnancy, microcythaemia, stress

INTRODUCTION

Since the first report by Confortini *et al.* who described a successful pregnancy in 1971, pregnancy on dialysis is still a rare and meaningful event that has been described as a clinical challenge, a miraculous occurrence or a revenge of life versus a chronic, intrusive, life-long disease [1–3].

Although epidemiological data are scant, there are a few basic tenets on pregnancies on dialysis. Results have greatly improved over time, with a gain in fetal survival of ~25% per decade, resulting in up to over 90% of live-births being reported in a recent Canadian series thanks to high efficiency, long-nocturnal haemodialysis, thus pointing to increasing dialysis efficiency as a tool for success [4–12]. Despite the overall improvement in results, placental insufficiency and pre-term delivery—often with fetal growth restriction (FGR)—are frequent, if not the rule. Thus, while there is overall agreement regarding the absence of increased risks of malformations in ‘dialysis children’, the long-term consequences of prematurity may represent important challenges for a child and a family that is already challenged by a chronic disease [4–12].

The issue of prematurity and of small babies is complex, as both situations are heterogeneous and may reflect different pathological events, in turn affecting the long-term development of the offspring differently. In fact, a small baby may be adequate for gestational age, and thus not exposed to the consequences of hypoxia or placental insufficiency, or may be small for gestational age (SGA), and slowly and harmonically growing along his/her own growth curve, or may develop progressive intrauterine growth retardation. All of these conditions usually reflect pathological acute or sub-acute interference with the physiological growth [13–15].

To the best of our knowledge, however, the only available studies regarding the children of dialysis mothers have mainly been aimed at assessing the risks of kidney disease in the offspring [16–19].

The pathophysiological challenges of prematurity on the developing kidneys and on the developing brain are increasingly acknowledged; however, the effect of prematurity on the overall well-being of children born to mothers on dialysis is not known. This overall view is crucial, as it may reflect the balance between the extraordinary power of compensation of human beings and the psycho-social effects of a chronic disease in a family member [20–25].

In this context, the aim of the present study is to evaluate the emotional and behavioural profile of the children and adolescents of mothers on chronic dialysis and the parental stress their mothers undergo as compared to a group of mothers affected by a different chronic disease (i.e. microcythaemia) and a group of healthy control mothers. We selected transfusion-dependent microcythaemia patients as the main control group. This choice was based upon the presence of several similarities (life-long disease, shorter life expectancy, frequent and regular admission to the hospital, frequent fertility impairment) and

differences (mothers on dialysis have a prospective of transplantation, dialysis is more time consuming than periodic transfusions, end-stage renal disease is not genetically transmitted), that might help us highlight the peculiarities of adaptation and response of on-dialysis mothers and their children [26–28].

MATERIALS AND METHODS

Patient selection: on-dialysis mothers

The present study was planned in the context of a nationwide analysis of the long-term results of pregnancy in dialysis patients who delivered between 2000 and 2012. In the absence of Registry data on pregnancy on dialysis, subjects were identified on the basis of capillary phone interviews with all the public dialysis centres in Italy as well as with the main private. The analysis was cooperative and was carried out by the Italian Study Group on Kidney and Pregnancy (Gruppo di Studio Rene e Gravidanza della Società Italiana di Nefrologia), in cooperation with the Italian Registry of Dialysis and Transplantation, and the National Association of Dialysis and Transplant patients (ANED), as described elsewhere in detail [29]. All data were acquired during 2013.

At this time, all the available mothers, and in case of the mother’s death, the father, were contacted and asked to participate to the study. Between 2000 and 2012, 23 on dialysis mothers had 23 pregnancies, resulting in 24 live-born babies (1 twin pregnancy, one of the twin deceased soon after delivery), at the time of the study 21 mothers were alive. In the case of the 2 deceased mothers, 1 father completed the interview, while the other had moved back to his homeland and was not found at time of study. Of the 21 remaining mothers, 2 declined participation; the questionnaire was not proposed to 2 mothers whose children had died soon after birth and to 1 mother who had severe psychiatric problems antedating dialysis. The mother of twins was asked to fill the questionnaire for the living child.

Hence, overall, 17 interviews were available for assessment (completed from 16 mothers and 1 father), but one of the questionnaires (Child Behavior checklist, CBCL) was too incomplete to be assessed.

Controls: microcythaemia patients

Mothers with transfusion-dependent beta thalassaemia and drepanocytosis were selected from the two largest Italian centres for the care of microcythaemia patients (Turin and Cagliari), both of which are reference centres for large areas. Selection criteria included having delivered a live-born baby in the 2000–2012 period, being transfusion-dependent, and being willing to participate. In both settings, all women with these characteristics were contacted and all of them agreed to participate. Ten mothers having a total of 14 pregnancies (and 14 children, i.e. 14 questionnaires) were recruited from the Turin Unit; however, due to the larger number of cases available at the Cagliari Unit, in order to balance the data between the two settings, only the first mothers who agreed to participate were included in the present analysis (13 mothers, 17 pregnancies, 1 twin, i.e. 18 children, 18 questionnaires).

Twenty-one women (29 children) had transfusion-dependent thalassaemia major and 2 women (3 children) transfusion-dependent drepanocytosis. Overall, 31 questionnaires were available for the final evaluation, but one of the questionnaires (CBCL) was too incomplete to be assessed.

Controls: healthy population

A control group made up of 35 mothers was selected. This subset of subjects was recruited from among the hospital workers and their families and friends on a volunteer basis. Selection criteria included having a pregnancy between 2000 and 2012, had a live-born, healthy baby and the absence of any known chronic disease. Each mother filled one questionnaire for one child aged 18 months to 18 years (35 questionnaires).

Questionnaires

The Child Behaviour Checklist. The CBCL was used to rate children and adolescents' behavioural and emotional problems [30]. The CBCL is an extensively used questionnaire that has also been validated for Italian children [31,32]. Chronbach's α is 0.8, witnessing acceptable internal consistency. There are two versions of the checklist: the pre-school checklist (CBCL 1½–5 years) for children aged 18 months to 5 years and the school-age version (CBCL 6–18) for children aged 6–18 years. Mothers are asked to complete the checklist on the basis of their perception of their child's behaviour. Each item is evaluated on a 3-point Likert scale (from 0 = 'not true' to 2 = 'very true or

often true'). The questionnaire provides scores for three broad-band scales: internalizing symptoms, externalizing symptoms and total behavioural problems and also for Diagnostic and Statistical Manual (DSM)-oriented scales. Definitions and examples of symptoms of the syndrome and DSM-oriented CBCL scales are shown in Table 1.

Raw scores for each clinical factor were transformed into T-scores based on published norms [30, 33, 34]. T-scores >63 were considered indicative of clinical impairment for the three broad-band scales, T-scores ≥ 70 were considered indicative of clinical impairment for syndrome scales.

The choice of the CBCL questionnaire, involving the parents without need for involving the children, was in line with a minimally invasive approach, and ensured, given the small number of cases, a homogeneous approach.

Parent Stress Index-Short Form. The Parent Stress Index-Short Form (PSI-SF) is a 36-item validated questionnaire on a 5-point scale showing good validity and reliability [35–38]. It measures parental stress through three sub-scales: parental distress (PD), measuring an impaired sense of parental competence and depression, parent-child dysfunctional interaction (P-CDI), intended to measure unsatisfactory parent-child interactions and difficult child (DC), measuring behavioural characteristics of the child that make him/her easy or difficult to manage.

Each item is evaluated on a 4-point Likert scale (from 0 = 'not true' to 3 = 'very true or often true').

Table 1. Syndrome scales and DSM-oriented scales of Child Behaviour Checklist (CBCL): definitions and symptoms

Syndrome scales: examples of typical problems by syndrome subcategory	
Internalizing symptoms	
Emotionally reactive ^a	Twitching, sulking, whining, worry, panic, rapid shifts in mood, upset by new situations/change
Anxious/depressed	Dependent, feelings easily hurt, upset by separation, looks unhappy, nervous, self-conscious, fearful, sad
Somatic complaints	Complains of aches and pains, headaches, stomachaches, diarrhoea, nausea, vomiting, not eating
Withdrawn	Acts immature, avoids eye contact, does not answer, little emotional expression or reaction, little interest
Externalizing symptoms	
Aggressive behaviour	Difficulty concentrating, wanders, can't sit still, clumsy, shifts quickly
Attention problems ^a	Defiant, demanding, destructive, disobedient, no guilt, frustrated, fights, angry moods, stubborn, uncooperative, attention-seeking, can't wait
Rule breaking behaviour ^b	Drinks alcohol, no guilt breaks rules, hangs around with others who get in trouble, lying or cheating, prefers being with older children, runs away from home, sets fires, sexual problems, steals, obscene language
Total behavioural problems	Combination of both internalizing, externalizing symptoms and 30 additional items for the CBCL 1½–5 or 17 for the CBCL 6–18 that do not load for any of the individual scales, plus the following standalone items
Sleep problems ^a	Difficulty sleeping alone, nightmares, resists going to bed, talks in sleep, wakes often, general loss of sleep
Social problems ^b	Dependent on adults, complains of loneliness, not get along, easily jealous, feels others out to get him, gets hurt a lot, teased a lot
Thoughts problems ^b	Can't get mind off certain thoughts, attempt suicide, hears sounds or voices that aren't there, twitching, picks skin, repeats acts, sees things
Attention problems ^b	Defiant, demanding, destructive, disobedient, no guilt, frustrated, fights, angry moods, stubborn, uncooperative, attention-seeking, can't wait
Diagnostic Statistical Manual (DSM)-oriented scales: examples of typical problems by diagnostic code	
Affective problems	Cries, sleep problems, looks unhappy, over or under eats, tired, low sleep, sad, little interest, underactive
Anxiety problems	Dependent, difficulty sleeping alone, fearful, nervous, upset by separation, worries, panic, nightmares
Somatic problems ^b	Physical problems such as aches, headaches, nausea, rashes or skin problems, problems with eyes, stomachaches, vomiting
Attention deficit/hyperactivity problems	Poor concentration, can't sit still, can't wait, demanding, gets into things, shifts quickly
Oppositional defiant problems	Defiant, disobedient, angry moods, stubborn, hot-tempered, uncooperative
Conduct problems ^b	Cruel to animals, cruelty, bullying, destroys things belonging to others, no guilt, breaks rules, fights, vandalism
Pervasive developmental problems ^a	Upset by new things/change, avoids eye contact, does not answer, does not get along with others well, rocks head, little emotional expression or reaction, speech problem, strange behaviour, withdrawn

^aOnly for CBCL 1½–5.

^bOnly for CBCL 6–18.

The total PSI-SF score is an indicator of the overall experience of parenting stress [35, 36, 38]. For each sub-scale, a score between the 15th and 85th percentile is considered normal; a score ≥ 85 th percentile represent a 'clinically significant' level of parenting stress.

Moreover, the PSI-SF comprises a sub-scale defined as 'Defensive Responding', which evaluates the extent to which the parent is trying to answer in a way he/she thinks may be rated as 'the best'. Parents with low scores on this scale may be trying to minimize problems and stress in their relationship with their child. A score of 10 or less indicates a defensive response and suggests caution in interpreting the stress scores.

Definitions and statistical analysis

Definitions. SGA babies were defined according to the Parazzini scores, as described elsewhere in detail [39]. Height and weight were assessed by the WHO internationally validated charts (www.who.int) and the classical Tanner–Whitehouse charts. The latter were chosen because of their widespread use throughout the study period [40]. Severe clinical problems in pregnancy were defined as those requiring at least two hospitalizations, beside those for delivery.

Statistical analysis. Normally distributed variables were expressed as mean and standard deviation, non-normally distributed data as median and 25th and 75th percentile, and binary data as percentage. Comparisons between two independent groups were made by *T*-test (normally distributed data), Mann–Whitney *U*-test (non-normally distributed data) or χ^2 test (binary data), with Fisher correction when appropriate. Comparisons between the three groups for non-normally

distributed data were made by Kruskal–Wallis analysis. A *P* < 0.05 was considered statistically significant. Data were analysed using IBM-SPSS (©IBM).

Ethical issues

The study protocol was approved by the ethics committee of the University of Turin (Azienda Sanitaria Ospedaliera San Luigi; delibera del Direttore Generale n.364, 17 June 2013).

All participants provided informed consent protecting the anonymity of the data; when the mother was unavailable, the father, asked to participate, provide consent.

RESULTS

Baseline data

Table 2 provides the main clinical characteristics of the two groups of mothers. In both cohorts, median age was not significantly different from the healthy control mothers (median 35 years; 25th centile: 31 years; 75th centile 35 years).

None of the women on dialysis had more than one pregnancy. Conversely, eight transfusion-dependent women had two pregnancies during the study period, one was a twin pregnancy.

Pregnancy occurred spontaneously in all the on-dialysis mothers and in the healthy controls. Conversely, assisted procreation procedures were needed in 11 transfusion-dependent women: 5 in Cagliari and in 6 in Turin.

The prevalence of pre-term and early pre-term babies was higher in on-dialysis mothers (all of the children, except one, were born pre-term) when compared with microcythaemia

Table 2. Main clinical features of the mothers and children included in the study in the dialysis-dependent and transfusion-dependent cohorts

	On-dialysis mothers	Microcythaemia mothers	P
Mothers			
No. of subjects	17	23	–
No. of pregnancies	17	31	
Age at start of dialysis or of blood transfusions: years (mean \pm SD)	28 \pm 5	2 \pm 2	<0.001
Age at delivery: years (mean \pm SD)	33 \pm 6	32 \pm 4	0.899
Maternal problems requiring at least two hospitalizations in pregnancy (%)	58.8	21.9	0.013
Early pre-term <34 weeks (%)	58.8	6.3	<0.001
Late pre-term 34–37 weeks (%)	35.3	21.9	0.498
All pre-term (%)	94.1	28.2	<0.001
Birth weight (median (min–max))	1450 (900–2250)	2450 (1200–3750)	<0.001
Children			
Subjects (questionnaires)	17	32	
Male (<i>n</i>)	8	16	0.998
Age (at the time <i>e</i> of interview) median (range)	8.5 (2–13)	7 (1–13)	0.701
No. of pre-school children, aged <6 years (CBCL 1½–5)	6	8	0.448
No. of children in grades 1–8th (CBCL 6–13)	11	24	
Centile: median (min–max)	33 (1–93)	38 (1–97)	0.580
SGA [<10th Centile (%)]	29	25	0.356
NICU (%)	64.7	6.3	<0.001
Main problems after birth (%)	11.8	9.4	0.294
Height <3rd centile (%)	5.9	6.3	0.615
Weight <3rd centile (%)	11.8	6.3	0.574
Weight and height <3rd centile	5.9	9.4	0.568

SGA: small for gestational age baby (Parazzini scales); NICU: Neonatal Intensive Care Unit; centiles in children are calculated according to the Tanner–Whitehouse scores.

Note: by definition, all healthy controls are born at term from physiological pregnancies.

None of the children had chronic disease or permanent disability, except for minor arm dysplasia in one child from on-dialysis mother (premature –26 weeks, male child, 10 years old at the time of study).

mothers. Conversely, the prevalence of SGA babies was not higher in children of on-dialysis mothers when compared with the children of microcythaemia mothers (Table 2).

In both cohorts, pregnancy resulted in an intensification of care: dialysis was increased in all patients, from a median of 3 times per week to a median of 6 times per week. Likewise, the frequency of transfusions increased during pregnancy in 11/13 cases in Cagliari (from a median of every 21 days to 10–15 days, reaching once a week in two cases) and in all cases in Turin (median transfusion interval: every 10 days).

As a reflection of the high incidence of prematurity, the children of on-dialysis mothers had more initial hospitalizations in the neonatal intensive care unit. However, the majority of patients were above the third percentile for age (height and weight) (Table 2).

All of the children from control mothers were healthy and born at term and all were above the third centile for height and weight.

The Child Behaviour Checklist

Overall data. Table 3 reports the results of the CBCL questionnaire. The three broad-band scales (internalizing, externalizing and the combination of these two, i.e. total problems) show a significant difference in total problems among the three groups; the difference is mainly due to a higher prevalence of anxiety/depression in microcythaemic mothers when compared with on dialysis and control mothers.

Other significant differences among the three groups are recorded in the three sub-scales affective, anxiety and attention deficit/hyperactivity problems (ADHD) shared by the two CBCL forms (age ½–5 and age 6–18 years), on pervasive developmental problems, specific for children aged ½–5 years and on social problems and problems regarding thoughts for older children (age 6–18 years).

In more detail, the mothers in the microcythaemia group reported a higher degree of anxiety on two DSM-oriented CBCL sub-scales (i.e. affective problems, anxiety problems) when compared with healthy mothers and to on-dialysis mothers. The differences between social, thought, affective and ADHD problems are significant between mothers in the microcythaemia group and healthy controls.

Conversely, the parents in the dialysis group were overall similar to the healthy controls. The only statistically significant difference between these two groups was observed for pervasive developmental problems that are characterized by delays in the development of socialization and communication; autism is the best known of these disorders (Figure 1).

Schooling was within the normal range for all children of on-dialysis and microcythaemic mothers. However, two of the children of dialysis mothers and one child born to a transfusion-dependent mother were reported to have socialization problems at school (versus none of the control children *p*: ns).

CBCL single profiles. Two children from on-dialysis mothers presented a T-score indicative of clinical impairment: one child presented a wide range of behavioural and emotional problems (i.e. withdrawn, social problems, attention problems, internalizing symptoms, externalizing symptoms, total problems, anxiety problems and ADHD) and one child was reported with less severe problems (i.e. attention problems, internalizing symptoms, total problems and ADHD).

The prevalence was not significantly different in the children of microcythaemia mothers, where three children had T-scores indicative of clinical impairment: one presented a wide range of problems (i.e. anxious/depressed, somatic complaints, attention problems, internalizing problems, total problems, affective problems and anxiety problems) and two less severe problems

Table 3. Results of the Child Behaviour Checklist (score)

Problems rated by the scale	On-dialysis mothers Median (25th and 75th pct)	Microcythaemia mothers Median (25th and 75th pct)	Healthy control mothers Median (25th and 75th pct)	P
Internalizing	48.0 (39.50–60.50)	56.0 (48.00–63.00)	50.0 (37.00–58.00)	0.061
Externalizing	47.0 (41.50–51.00)	49.0 (44.00–56.00)	49.0 (37.00–56.00)	0.498
Total behavioural problems	48.5 (39.25–57.25)	53.0 (46.00–58.00)	49.0 (36.00–54.00)**(0.010)	0.031
Emotionally reactive ¹	50.5 (50.00–56.00)	50.0 (50.00–55.00)	50.0 (50.00–50.75)	0.648
Anxious/depressed	50.0 (50.00–59.75)	54.0 (51.00–63.00)*(0.029)	51.0 (50.00–57.00)**(0.005)	0.010
Somatic complaints	53.0 (50.00–60.75)	57.0 (53.00–62.00)	53.0 (50.00–59.00)	0.172
Withdrawn	51.0 (50.00–61.25)	51.0 (50.00–58.00)	50.0 (50.00–54.00)	0.334
Aggressive behaviour	50.0 (50.00–53.75)	51.0 (50.00–57.00)	51.0 (50.00–55.00)	0.581
Attention problems	51.0 (50.00–59.75)	52.0 (50.00–57.50)	51.0 (50.00–57.00)	0.752
Rule breaking behaviour ²	51.0 (50.0–55.50)	50.5 (50.00–52.25)	50.0 (50.00–51.00)	0.449
Sleep problems ¹	54.5 (50.00–60.25)	53.0 (50.50–59.00)	52.5 (50.00–63.50)	0.920
Social problems ²	51.0 (50.00–61.50)	53.5 (51.00–61.25)	51.0 (50.00–54.00)**(0.008)	0.035
Thought problems ²	50.5 (50.00–53.50)	52.0 (50.00–64.00)	50.0 (50.00–51.00)**(0.010)	0.031
Affective problems	50.0 (50.00–52.00)	52.0 (51.00–63.00)*(0.007)	50.0 (50.00–54.00)**(0.001)	0.001
Anxiety problems	50.0 (50.00–60.00)	59.0 (51.00–68.00)*(0.035)	51.0 (50.00–58.00)**(0.004)	0.009
Somatic problems ²	50.0 (50.00–51.50)	56.0 (50.00–64.25)	50.0 (50.00–56.00)	0.051
Attention deficit/hyperactivity problems	50.5 (50.00–55.75)	51.0 (50.00–60.00)	50.0 (50.00–52.00)**(0.005)	0.023
Oppositional defiant	51.5 (50.00–54.25)	51.0 (50.00–55.00)	51.0 (50.00–52.00)	0.550
Conduct problems ²	50.5 (50.00–55.25)	50.0 (50.00–53.25)	50.0 (50.00–51.00)	0.321
Pervasive developmental problems ¹	56.0 (50.75–60.75)***(0.005)	50.0 (50.00–54.00)	50.0 (44.25–50.00)	0.005

¹ only for CBCL 1½–5 ² only for CBCL 6–18.

*MW (Mann-Whitney test): microcythaemia versus dialysis significant *P* < 0.05.

**MW: microcythaemia versus healthy controls significant *P* < 0.05.

***MW: Dialysis versus healthy controls significant *P* < 0.05.

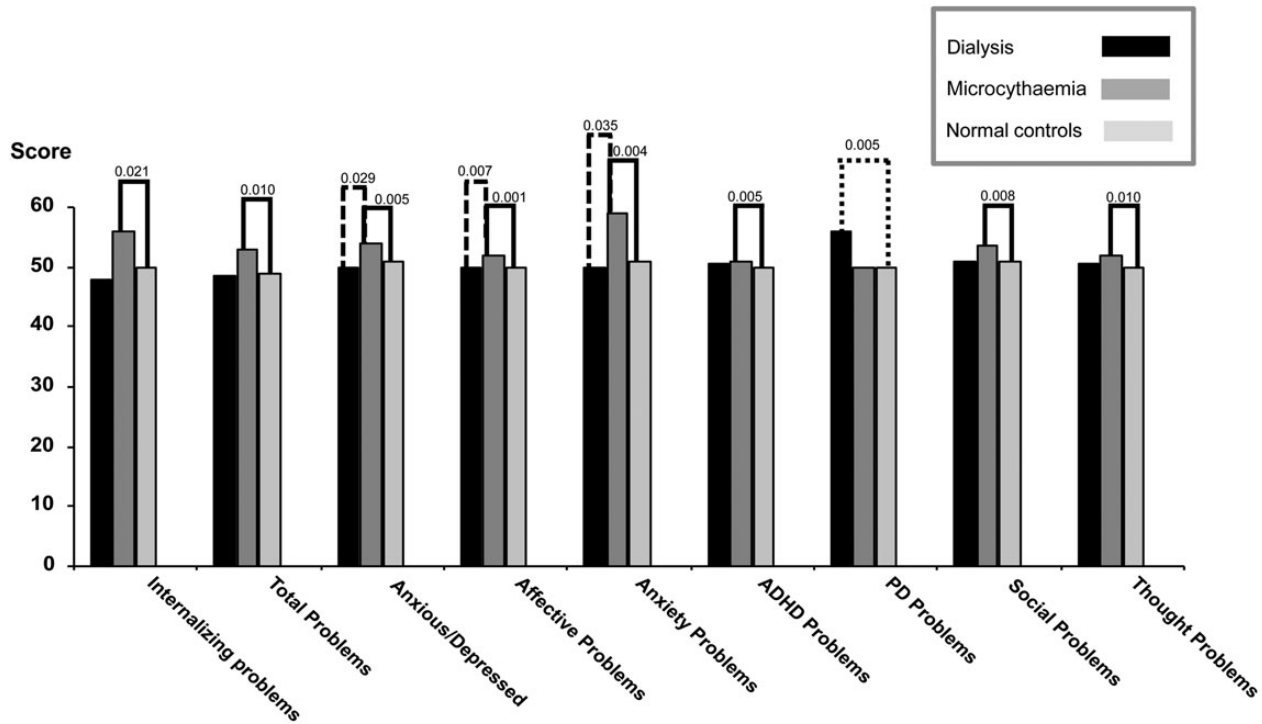


FIGURE 1: Median score of CBCL items significantly different among the three groups. MW test: microcythaemic versus dialysis; MW, microcythaemic group versus normal controls; MW, dialysis versus normal controls.

Table 4. Parent Stress Index-Short Form (percentiles)

	On-dialysis mothers Median (25th and 75th pct)	Microcythaemia mothers Median (25th and 75th pct)	Healthy control mothers Median (25th and 75th pct)	P
Parental distress	10.0 (3.00–30.00)	50.0 (35.00–70.00)*(0.002)	50.0 (35.00–60.00)**(0.001)	0.002
Parent–child dysfunctional interaction	10.0 (5.00–35.00)	50.0 (31.25–70.00)*(<0.001)	50.0 (35.00–55.00)**(<0.001)	<0.001
Difficult child	20.0 (5.50–35.00)	50.0 (35.00–65.00)*(0.005)	45.0 (30.00–55.00)**(0.007)	0.007
Total score	10.0 (1.00–27.50)	47.5 (21.25–70.00)*(<0.001)	45.0 (30.00–50.00)**(<0.001)	<0.001

*MW (Mann–Whitney test): microcythaemia versus dialysis significant $P < 0.05$.

**MW: microcythaemia versus healthy controls significant $P < 0.05$.

(i.e. one with attention problems, affective problems and ADHD and one with anxious/depressed and anxiety problems). None of the control children had pathologic profiles.

Parent Stress Index-Short Form

Table 4 summarizes the results of the PSI-SF.

The results show significant differences among the three groups with regard to PSI total score ($P < 0.001$) and to all PSI sub-scales (PD, P-CDI and DC).

Specifically, the microcythaemia mothers experience similar levels of parental stress as healthy mothers, and both groups perceive a higher degree of parental stress when compared with mothers on dialysis.

The level of parental stress is slightly higher in microcythaemia mothers, although it is still within the normal range (clinical impairment is considered to be present only above the 85th percentile).

Furthermore, in the dialysis group, 8/16 parents with evaluable questionnaires (50%) reported a score of 10 or less in the PSI sub-scale that is considered indicative of a defensive response, when compared with 4/23 mothers in the

microcythaemia group and to 3/35 of the healthy mothers (Fisher's exact test: $P = 0.041$ dialysis versus microcythaemia; $P = 0.002$ dialysis versus controls). This pattern suggests a defensive tendency of the on-dialysis mothers to minimize problems, stress, or negativity in their relationship with their child. The answers of the father whose wife died were in line with the other answers of the dialysis group, including also the defensive response that may have been motivated by his still recent loss.

DISCUSSION

In the care of chronic diseases affecting young women, many patients and physicians consider the goal of pregnancy a crucial one, since a successful pregnancy demonstrates both the attainment of a physical balance good enough to support the development of a new human being, and the attainment of the 'physiological' social goal of creating a new family [1–3]. This may also be the case both for women on dialysis, for whom pregnancy may be considered a new clinical and social frontier, and for transfusion-dependent microcythaemia patients [41].

The latter were chosen since their chronic disease causes them to share several characteristics with patients on dialysis, such as a life-long disease and the need for hospital care, both of which also affect the odds of getting pregnant [9–12, 26–28].

The mother–child dyad is very complex. Even when it is considered a medical miracle, pregnancy in chronic diseases should not be expected to be ‘without a price’, both in terms of clinical risk and of psychological burden for the mother, which may be worsened by the presence of intellectual or behavioural problems in the child. The issue of parental stress, however, has never been extensively studied in most chronic diseases, including end-stage kidney disease. Very few studies have addressed this issue for other chronic illnesses, such as Thalassaemia, HIV positivity or rheumatic disorders [41–45]. The issue of behavioural problems in the children of these mothers is even more complex, as it may be influenced, to various degrees, by the underlying maternal disease, by prematurity and other related issues, such as very low birth weight or ‘small for gestational age’ and, not least, by maternal-familial stress [45–50]. To date, this complex problem has never been studied in pregnancy on dialysis, also because of the rarity of this event [7–11, 29].

The main results of our study are encouraging: the overall outcome of the children of on-dialysis mothers is good, both from the physical and from the psychological point of view (Tables 2–4). In fact, at the time of our inquiry, we observed a low prevalence of children of on-dialysis mothers in low height and/or weight centiles despite the high prevalence of babies who were born pre-term and, most importantly, we observed no severe disabilities among the children we analysed (Tables 2 and 3) [29].

With regard to behavioural problems, the answers to the parenthood questionnaires that were given by the dialysis mothers were similar to those given by the healthy control group: the only statistically significant difference was recorded for pervasive developmental problems (Table 4). The pervasive disorders are characterized by delays in the development of several basic functions including socialization and communication and are closely related to autism, the best-known disease of this group [51, 52].

It may be worth mentioning that this family of behavioural disorders has been associated with pre-term delivery, very low birth weight, maternal hypoxia and various maternal problems in pregnancy [53–55]. The long-term consequences of maternal diseases and of placental dysfunction have only recently started to be unravelled; hence, while it is probably too early to include information in routine counselling, the uncertainties on this issue should probably be mentioned [56].

However, the presence of a higher score is not *per se* synonymous of overt disease, and, indeed, only two children from on-dialysis mothers had overall pathologic profiles at the test (one severe, one mild). The prevalence of pathologic scores is similar in children of transfusion-dependent microcythaemia mothers (three children, one with severe and two with milder problems).

Despite the above-mentioned similarities between dialysis dependency and transfusion dependency, the results differed significantly between the two groups, the latter reporting greater emotional and behavioural problems in their children

(Table 3). Again, the presence of higher scores is not *per se* synonymous of overt disease, but the typology of problems may suggest the need for support interventions for the families.

An analysis of parental stress offers some further interesting insights (Table 4). According to the results of the PSI-SF, mothers on dialysis declared a significantly lower degree of parental stress when compared with both control groups; the overall scores are, however, within the normal range.

Interestingly, half of the parents in the on-dialysis group reported a score of 10 or less in the PSI sub-scale, which is indicative of a defensive response. An analogous response was present in only 4/23 mothers in the microcythaemia group ($P = 0.041$) and in 3/35 healthy mothers ($P = 0.002$). This finding suggests that on-dialysis mothers may tend to minimize the problems they may encounter in their relationship with their children. A straightforward interpretation of this response is not possible at present. It may highlight a form of defence by denying the problems, in this specific case, related to the stress of parenthood. This type of defence was described in dialysis patients at the start of the renal replacement therapy era, more than four decades ago, and was recently reconfirmed in dialysis patients, as well as in patients affected by other chronic diseases [57–62]. On the other hand, pregnancy on dialysis is exceptional and we cannot exclude that this response is simply part of the personality of strong women who are able to face difficult problems and who may rate difficulties in a different way, when compared with women who did not experience dialysis. Whatever the reason, this attitude should be taken into consideration when offering tailored psychological help to mothers on dialysis, and should be kept in mind during pre-conception counselling, together with the fact that, in line with the results of the overall dialysis cohort, long-term maternal mortality is still high (8.9% over the 13 years of follow-up) [63].

Our study has some strengths: first of all its novelty, and more importantly the enrolment of a control group made up of subjects with a different chronic disease, indirectly suggesting that dialysis patients may respond to their limitations in very specific ways.

Our study also has several limitations: it includes a relatively small number of subjects; nonetheless, it is one of the largest series published to date that includes children born in the new millennium to on-dialysis mothers [2–12, 29]. The small number of subjects impairs stratification for clinical determinants, such as the degree of prematurity, birth weight or perinatal complications, maternal disease, or educational income levels. Such a detailed analysis could be the next step, further extending the study to other countries, possibly enrolling also different controls groups of mothers with other chronic diseases and/or of premature babies.

Furthermore, the choice of a questionnaire filled in by the parents, such as the Child Behaviour Checklist, does not allow us to distinguish between the pathologic responses of parents and children, and may be considered less ‘objective’ than a test that is directly performed with the children. However, we decided to implement this validated tool in order to minimize the intrusiveness of our inquiry, also keeping in mind that in such a new field a first study is mainly aimed at identifying the issues that future analyses should focus on.

CONCLUSIONS

The emotional and behavioural outcome of children of on-dialysis mothers is within the normal range in most cases, a result that is shared with the other chronic disease chosen as the control (transfusion-dependent microcythaemia). However, despite a good general outcome, 2/17 children of on-dialysis mothers versus 3/32 children of microcythaemia mothers had pathologic profiles, thus underlining the need for planning tailored support interventions during and after pregnancy in women affected by chronic diseases.

Particular attention should be paid to pervasive developmental disorders, mainly involving communication skills, in children of on-dialysis mothers and to anxiety in the children of microcythaemia mothers.

The lower rate of parental stress in on-dialysis mothers may at least be partly due to a 'positive defense', resulting in denial of the children's problems: further studies are needed on this issue, employing also different psychological scales, and psychometric tools. Such behaviour should also be kept in mind when tailoring psychological support for this 'medical miracle'.

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CONFLICT OF INTEREST STATEMENT

None declared.

APPENDIX

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Gram-negative bacteraemia in haemodialysis

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ABSTRACT

Background. Patients on renal replacement therapy experience higher rates of morbidity and mortality, infection being the second commonest cause of death. In our haemodialysis population, we identify the pathogens, sensitivity patterns, sources of infection and outcomes of Gram-negative bacteraemia.

Methods. Data from the NHS Greater Glasgow & Clyde and NHS Forth Valley haemodialysis population were collected July 2011 to April 2014 through an interrogation of the renal unit electronic patient record, and confirmed by an independent search of the Microbiology database.

Results. Over 544 377 haemodialysis days, 84 patients experienced 95 Gram-negative bacteraemia events, a rate of 0.175 events per 1000 haemodialysis days, which varied with dialysis modality: non-tunnelled central venous catheters 4.77, arterio-venous grafts 0.24, tunnelled central venous catheters 0.21, and arteriovenous fistulae 0.11 per 1000 haemodialysis days. The commonest sources of bacteraemia were central venous catheters (CVCs) (16.8%, $n = 16$), infected ulcers (14.7%, $n = 14$), urinary (10.5%, $n = 10$), biliary (9.5%, $n = 9$) and intra-abdominal (9.5%, $n = 9$).

The principal organisms were *Escherichia coli* (49.5%, $n = 47$), *Enterobacter* spp. (13.1%, $n = 13$), *Klebsiella* spp. (11.1%, $n = 11$),

Proteus mirabilis (6.1%, $n = 6$) and *Pseudomonas aeruginosa* (5.1%, $n = 5$). Of the Enterobacteriaceae ($n = 84$), 88% were sensitive to gentamicin, 81% to ciprofloxacin, 91% to piperacillin-tazobactam and 100% were sensitive to meropenem.

Three-month case mortality was 25.3% ($n = 24$). Ten patients (11.9%) had more than one Gram-negative bacteraemia; of these, nine patients (90.0%) were the same causative organism, predominantly *E. coli*.

Conclusions. CVCs and diabetic foot ulcers remain significant risk factors for Gram-negative bacteraemia, highlighting the importance of vascular access planning. Despite good levels of antibiotic sensitivity, the early mortality following Gram-negative bacteraemia remains high, supporting aggressive treatment of such pathogens.

Keywords: bacteraemia, Gram-negative, haemodialysis, sensitivity, vascular access

INTRODUCTION

It is well established that the rates of morbidity and mortality are significantly higher for patients on renal replacement therapy (RRT) in comparison to the general population; for example, in the UK the mortality rate for RRT patients aged