32. Shor R, Halabe A, Rishver S *et al.* Severe hypophosphatemia in sepsis as a mortality predictor. *Ann Clin Lab Sci* 2006; 36: 67–72
33. Zipf WB, Bacon GE, Spencer ML *et al.* Hypocalcemia, hypomagnesemia, and transient hypoparathyroidism during therapy with potassium phosphate in diabetic ketoacidosis. *Diabetes Care* 1979; 2: 265–268
34. Markowitz GS, Stokes MB, Radhakrishnan J *et al.* Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. *J Am Soc Nephrol* 2005; 16: 3389–3396

Received for publication: 30.11.10; Accepted in revised form: 25.1.11

Nephrol Dial Transplant (2011) 26: 3514–3522
doi: 10.1093/ndt/gfr046
Advance Access publication 9 March 2011

Respiratory and general outcome in neonates with renal oligohydramnios—a single-centre experience

Katrin Mehler[1,*], Bodo B. Beck[2,3,*], Ingrid Kaul[4], Gohar Rahimi[5], Bernd Hoppe[2] and Angela Kribs[1]

[1]Division of Neonatology and Paediatric Intensive Care Medicine, Children's Hospital, University of Cologne, Cologne, Germany, [2]Divison of Paediatric Nephrology, Children's Hospital, University of Cologne, Cologne, Germany, [3]Institue of Human Genetics, University of Cologne, Cologne, Germany, [4]Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Cologne, Germany and [5]Department of Gynaecology and Obstetrics, University of Cologne Medical Centre, Cologne, Germany

Correspondence and offprint requests to: Katrin Mehler; E-mail: katrin.mehler@uk-koeln.de
*These authors contributed equally to this work

Abstract

Background. Renal oligohydramnion (ROH) is predominantly caused by congenital abnormalities of the kidney and urogenital tract (CAKUT). Although the number of neonates born with chronic renal failure is small, they provide many challenges, and among the most problematic are respiratory management and long-term treatment of chronic renal failure. We studied the value of prenatal and perinatal variables to predict survival and the general long-term outcome of our ROH population.

Method. A single-centre retrospective chart review was conducted in 36 neonates with ROH treated between 1996 and 2007. Respiratory data sets including minimum inspiratory oxygen concentration (FiO_2, 1d), best oxygenation index (BOI, 1d) and minimum arterial partial carbon dioxide (pCO_2, 1d) at the first day of life were available in 23 children requiring intubation.

Results. ROH causes were obstructive uropathy ($n = 19$), polycystic kidney disease [autosomal recessive polycystic kidney disease (ARPKD) $n = 5$ and autosomal dominant polycystic kidney disease $n = 1$], renal agenesis/dysplasia ($n = 10$) and bilateral renal vein thrombosis ($n = 1$). Survival until discharge was 64% (23/36), and overall survival was 58% (21/36). Seven patients died within 48 h from respiratory failure. Non-survivors had a higher minimum FiO_2 and pCO_2 (1d) compared to survivors ($P < 0.001$). Mean BOI (1d) was 6.2 in survivors versus 43.9 in the non-surviving group ($P < 0.001$). Logistic regression showed that BOI ($</\geq 9.6$) and first diagnosis of ROH ($\leq/>28$ gestational weeks) retained significance in predicting survival until discharge.

Conclusions. The attitude toward initiating dialysis in neonates is changing and long-term outcome in the absence of severe comorbidity is promising. Prenatal prediction concerning respiratory and renal outcome in fetuses with ROH is difficult. Our data suggest that BOI (1d) and onset of ROH may be reliable predictors of respiratory prognosis in children born with ROH.

Keywords: best oxygenation index; chronic renal failure; congenital renal failure; pulmonary hypoplasia; renal oligohydramnios

Introduction

Before the 1970s, performing renal replacement therapy (RRT) in children with end-stage renal failure (ESRF) was mostly paediatric unethical. As a result of the progress in paediatric intensive care medicine, proven favourable long-term outcome as well as adaptations of RRT techniques to paediatric needs, dialysis and subsequent transplantation is offered to most children today [1–6].

Congenital abnormalities of the kidney and urogenital tract (CAKUT) are frequently detected antenatally in ~1% of children [7]. Bilateral disease that results in renal oligohydramnion (ROH) indicates relevant renal function impairment and implies a substantial risk both for renal dysfunction and for pulmonary complications (hypoplasia). Next to structural abnormalities of the vast CAKUT spectrum, autosomal recessive polycystic kidney disease (ARPKD), bilateral renal venous thrombosis, cortical

necrosis and many more conditions may present with ROH on fetal ultrasound scans [7–9].

There are conflicting data on the prognostic impact of ROH and the consequences of prenatal diagnosis. In older series, prognosis was mostly regarded as poor and all or most children with CAKUT and ROH died [10–12]. Other series report more encouraging survival rates. This is especially true for cases where fetal lung development is not or only mildly affected [9, 13–16]. One would expect that the wide usage of antenatal fetal ultrasound will lead to more terminations for potentially lethal renal anomalies resulting in declining numbers of patients with ROH. Not surprisingly terminations seem to be frequent practice in some institutions [17].

Others report the opposite situation with parents demanding all available treatment and not opting for pregnancy termination or postpartal palliative care [4].

Despite the enormous progress made in paediatric intensive care and the wide availability of modern ventilation techniques, respiratory stabilization is still a challenge in some babies with ROH and lung hypoplasia. Pulmonary hypoplasia is believed to originate directly from impaired development and maturation of pulmonary azini. In a series of 850 perinatal autopsies, lung hypoplasia was most common found in association with renal agenesis followed by diaphragmatic hernia [18–20].

The main aim of our study was to investigate the value of pre- and postnatal paediatric variables with special focus on the early respiratory and general survival in our ROH cohort.

Materials and methods

Study population

This study is a single-centre retrospective analysis of infants with antenatally diagnosed ROH treated at our institution from October 1996 to October 2007. Our hospital provides a Level III B neonatal intensive care unit (NICU) and is the primary regional centre for paediatric RRT.

A total of 36 live-born infants (30 males and 6 females) with ROH were analysed using retrospective chart review. Thirty-one babies were born at the University of Cologne Medical Centre and five were outborn neonates transferred for further respiratory and renal management. Individual patient characteristics are given in Table 1.

Definition of ROH was generalized reduction in amniotic fluid with two diameter pocket being <15 cm^2 in the presence of kidney and/or urogenital tract abnormalities [21]. All ultrasound investigations were performed by licensed sonographers being certified by the German Ultrasound Society for extensive experience in prenatal ultrasound (Deutsche Gesellschaft für Ultraschall in der Medizin e.V. Level III).

Causes of renal disease were as follows: most children suffered from CAKUT. Nineteen neonates had obstructive uropathy, among them 18 boys with posterior urethral valves (PUV) and 1 girl with urethral atresia and cloacal malformation. Two out of the 18 boys had prune belly syndrome (PBS) with associated comorbidities. The renal dysplasia/agenesia group ($n = 10$) included two infants with bilateral renal agenesis, six babies with bilateral renal dysplasia and two children with unilateral renal agenesis plus contralateral multicystic dysplastic. In addition, six infants suffered from polycystic kidney disease (five ARPKD and one autosomal dominant polycystic kidney disease) and a single child from fetal bilateral renal vein thrombosis. The diagnosis of ARPKD (next to having the characteristic clinical features) was indirectly established by showing linkage to the *PKHD1* locus in all five cases. Pre- and postnatal counselling was provided to all families (including outborn infants) by a team of senior paediatric nephrologists and neonatologists.

Ventilatory management. Mechanical ventilation was performed pressure controlled with a positive end expiratory preasure of 6–8 cm H_2O and peak inspiratory pressure (PIP) 20–25 cm H_2O. Frequency was set at 40–50/min. Bovine surfactant (100 mg/kg) was applied if an inspiratory fraction of oxygen of >0.4 was needed to establish an arterial pO_2 of >50 mmHg. Patients were switched to high-frequency oscillation (HFOV) if oxygenation or ventilation was still poor under conventional ventilation (maximum PIP 28–30 cm H_2O) to keep arterial pO_2 >50 mmHg, arterial pCO_2 <60 mmHg and pH >7.30. SensorMedics 3100A respirator (infants >3000 g) and Babylog 800 plus respirator (infants <3000 g) were used to apply HFOV. Infants were switched from HFOV to conventional ventilation if the mean airway pressure could be reduced <10 cm H_2O. Inhalative nitric oxide (iNO) (maximum dosage 20 p.p.m.) was applied if oxygenation did not improve or pulmonary hypertension was diagnosed by echocardiography.

Cardiovascular management. Normal saline or full electrolyte fluid flushes were given in order to keep the mean arterial blood pressure >40 mmHg in term and 35 mmHg in preterm infants. Vasopressor therapy was started with dopamine (DP) 3–8 μg/kg/min and dobutamine (DB) 5–10 μg/kg/min. If necessary, norepinephrine (ne) (0.1–1 μg/kg/min) and eventually epinephrine (e) (0.1–1 μg/kg/min) were added.

Data collection

Clinical information collected on each patient included gender, gestational age, birth weight, gestational week in which ROH was first noted, prenatal interventions, renal disease, extrarenal disease, respiratory outcome, presence of lung hypoplasia and pneumothorax on chest X-ray, ventilatory mode, time on mechanical ventilation, the use of nitric oxide and surfactant, renal outcome, timing and duration on RRT and vasopressor support.

On all inborn babies, blood gas and ventilatory data at the first day of life were analysed if infants required mechanical ventilation. The two neonates, whose parents opted not in favour of mechanical ventilation and therefore received only palliative care ($n = 2$), were excluded from further respiratory analysis. Arterial postductal blood sampling for gas analysis was performed at least every 4 h and minimum $PaCO_2$, best oxygenation index (BOI, d1) and minimum fractional inspired O_2 (FiO_2) within the first 24 h were determined from a series of blood gases. BOI was calculated from the best blood gas on Day 1 of life as [fractional inspired O_2 (in %) × mean airway pressure (in mbar)/PaO_2 (in mmHg)] [22].

The primary outcome was patient survival until time of hospital discharge. Prenatal (i.e. timepoint of ROH diagnosis, interventions, renal diagnosis) and postnatal parameters (i.e. birth weight, respiratory variables) were determined for their usefulness predicting early (respiratory) survival and late (survival to leave hospital) survival in ROH.

Statistical analysis

All parameters were characterized by descriptive statistics. Differences between survivors and non-survivors were evaluated using independent samples *t*-tests for continuous and chi-square tests for categorical data. For survival analysis, Kaplan–Meier curves were plotted and compared with the log-rank test. Logistic regression was employed to assess the impact of parameters on survival, expressed as odds ratio (OR) with 95% confidence interval (CI). A P-value <0.05 was considered to be statistically significant. The binary logistic regression model is a multivariate analysis accounting for the problem of multiple factors analysed on a $P = 0.05$ level. All computations were done using SPSS 17.0 software.

Results

A total of 36 neonates (30 males and 6 females) with ROH were treated during the study period. This number represents the complete set of ROH patients at our institution during the 11-year time span. Overt male predominance can be attributed to the large group of obstructive uropathies in this cohort. The number of pregnancy termination for ROH over that time period remains unknown to us. Table 1 gives individual clinical data and the number of live-born infants treated with ROH by year of birth.

All patients were admitted to the NICU for at least 24 h. Overall hospital mortality of the ROH population was 36% (13 of 36) with the majority of deaths occurring in the neonatal period (11 of 13, 85%). Figure 1 gives representation of survival in patients with ROH. Of the 11 patients who died in the neonatal period, 7 died due to respiratory failure within the first 48 h of life and initiation of dialysis therapy was attempted in none. Two patients died on Day 1 because intubation was withheld and palliative care was initiated (Table 1; Patients 30 and 31). The remaining two patients died primarily from renal failure on Days 5 and 6. Given the severity of the underlying renal disorder plus rather low birth weights, parents and physicians mutually agreed on withholding dialysis in these infants (Table 1; Patients 11 and 20).

Two patients died beyond the neonatal period but before discharge on Day 45 (Table 1; Patient 26) and on Day 61 (Table 1; Patient 3). The first patient with PBS and small bowel stenosis died from (procedure-related) intestinal perforation. The second patient experienced bacterial peritonitis as a complication and died after temporary haemodiafiltration (continuous venovenous hemofiltration).

Looking at the group of underlying renal condition, the renal agenesis/dysplasia cohort showed the worst (30%) and the obstructive uropathies the best survival rates (84%), placing the smaller polycystic kidney disease group right in the middle. Survival analysis (Figure 2) suggests that non-survival may be associated with the type of primary renal diagnosis, although the log-rank test did not reach statistical significance ($P = 0.167$). This is most likely due to the small number of patients. Logistic regression analysis showed borderline significance for survival being dependent on diagnosis (OR: 5, 95% CI: 1.1–23.1; $P = 0.039$).

Table 2 illustrates the association of prenatal and postnatal variables with survival until discharge. Non-survivors had significantly lower birth weight, earlier detection of ROH and more frequently a diagnosis classified as agenesis/dysplasia. Gender, gestational age, antenatal interventions (amnioinfusions and vesicoamniotic shunting), mechanical ventilation, duration of ventilation and presence of lung hypoplasia and pneumothorax did not reach significance.

For the early respiratory survival (first 24 h of life), data are shown in Table 3. In this analysis, only children that needed intubation and mechanical ventilation were included. Twenty-three of the 36 infants (66%) required mechanical ventilation for a median duration of 5 days (range 1–40 days). Three children needed only nasal continuous positive airway pressure for the first 24 h. Detailed respiratory data are shown in Table 3 including use of surfactant and iNO.

Minimum FiO_2, minimum pCO_2 and the best OI within 24 h of life showed significantly different values in survivors and non-survivors (see Table 3 and Figure 3). In patients who survived, normocapnia could be achieved within 24 h and FiO_2 could be reduced <0.4. All patients who survived beyond 24 h had a BOI of ≤ 9.6 compared to BOI values >24 in the group of non-survivors. Initial onset of ROH indicated borderline significance in predicting survival >24 h in ventilated infants ($P = 0.049$).

Logistic regression analysis showed that a BOI <9.6 increased chance of survival almost 16-fold (95% CI: 1.4–174.2), while onset of ROH beyond 28 weeks of gestation increased chance of survival 50-fold (95% CI: 4.5–551.4). Using both BOI ($</\geq 9.6$) and onset of ROH ($\leq/>28$ weeks) as independent variables, logistic regression analysis allowed the most accurate prediction of survival until discharge with ORs of 30 [BOI ($</\geq 9.6$), 95% CI: 1.4–647.4, $P = 0.029$], respectively, 75 [ROH ($\leq/>28$ weeks), 95% CI: 4.2–1362.0, $P = 0.003$] employing the following equation: $\ln(p/(1-p)) = 3414 \times \text{BOI}(</\geq 9.6) + 4321 \times \text{ROH}(\leq/>28 \text{ weeks}) - 2673$. To enable calculation, a BOI value of 9.6 was determined by design as cutoff since 9.6 discriminated perfectly between survivors and non-survivors.

Clinical relevant renal dysfunction was noted in 34 of the 36 neonates (94%). Severe renal dysfunction (anuria, hyperkalaemia, massive fluid overload) equivalent to end-stage renal disease (ESRD) occurred in all ($n = 13$) non-survivors [mostly not dialysed (except Patient 3 Table 1)] and in 8 survivors. In eight of nine cases, peritoneal therapy needed to be initiated within the neonatal period at a median of 8 days (range 2–24 days).

From the 23 children who survived until discharge, 7 started peritoneal dialysis (PD) within the neonatal period. In one child (Patient 15, Table 1), marked chronic renal insufficiency could be managed conservatively and peritoneal dialysis postponed until 13 months of life. Two of the children requiring neonatal RRT died at 21 months (Patient 8, Table 1) and 34 months (Patient 34, Table 1) of life, respectively, from complications (viral infection and complex syndromal disorder) unrelated to dialysis treatment. Altogether, four children received successful renal grafts at a median age of 25 months (range 23–52 months) including two children that required neonatal PD. In three patients from the neonatal PD group, need for dialysis was temporary and PD could be stopped after 1, 4 and 5 months, respectively. All three are currently managed conservatively, despite marked renal insufficiency and await cadaveric kidney transplantation. One child from the chronic kidney disease (CKD) group underwent pre-emptive living-related renal transplantation at the age of 4.4 years. From the remaining 14 children, renal function recovered to estimated glomerular filtration rate (GFR) within normal limits in 5 children. In the other nine children, CKD did not deteriorate to ESRD so far. From the eight infants presenting with extrarenal and/or complex chromosomal anomalies surviving until discharge, six are still alive including two children that underwent successful kidney transplantation.

Overall survival of our ROH series is 58% (21/36) after a median follow-up time of 96 months (range 30–152 months). Neurological outcome was only grossly assessed, 15 children showed normal or slightly impaired psychomotor skills, while 6 children developed moderate to severe psychomotor retardation.

Discussion

Our overall survival with antenatally diagnosed ROH is ~60%. There are centres reporting higher survival rates of

Table 1. Individual patient data[a]

Patient	Sex	Year	GA	BW	Renal dx	Extrarenal dx	ROH (gw)	MV (days)	Vasopressor support	Minimal FiO_2 (Day 1)	BOI (Day 1)	Start RRT (day)	Survival (s) death (day)	Long-term renal outcome
1	m	2007	31	1900	OU (PUV)	None	29	5	dp/db	0.7	9.1	0	s	Normal
2	m	2007	39	3680	OU (PUV)	Macrocephalus	32	14	dp	0.3	4.1	9	s	CKD
3	m	2007	32	1700	RA/DK	None	20	6	dp/db	0.21	2.2	2	d (61)	na
4	m	2007	31	1330	RA/DK	None	27	2	dp/db/ne	1	30	0	d (1)	na
5	m	2007	37	3260	ARPKD	None	32	1	None	1	45	0	d (1)	na
6	m	2007	39	3680	OU (PUV)	None	34	0	None	0.24	na	0	s	CKD
7	m	2007	33	3100	ARPKD	XXY mosaic, cardiac	32	13	None	1	5.2	3	s	KTX
8	m	2000	39	3500	OU (PUV)	None	38	0	None	0.21	na	0	s	Normal
9	m	1999	34	2530	KD bilateral	Del 22q11.2, cardiac	30	0	None	0.25	na	24	[c]d (630)	na
10	m	1996	37	3350	OU (PUV)	None	25	1	None	1	43	0	d (1)	na
11	f	2002	35	1200	RA bilateral	MMC	28	5	None	0.35	7	0	d (5)	na
12	m	2002	38	2850	OU (PUV)	None	27	4	dp/db	0.35	4	0	s	Normal
13	f	2001	34	2100	KD bilateral	None	20	1	dp/db	1	24	0	d (1)	na
14	m	1999	34	2160	OU (PUV)	None	29	0	None	0.21	na	0	s	CKD
15	m	1998	32	2250	OU (PUV)	None	29	5	dp	0.3	0.8	375	s	KTX
16	m	1998	36	2440	OU (PUV)	None	32	5	dp/db	0.35	9	0	s	CKD
17	f	1998	30	1270	OU (UA)	Cloacal malformation	29	21	dp/db	0.4	9	0	s	CKD
18	m	2001	35	3450	OU (PBS)	None	31	2	dp/db/ne	1	74	0	d (1)	na
19	m	2001	37	2530	OU (PUV)	None	22	1	dp/db/ne/e	1	29	0	d (1)	na
20	m	2001	30	1130	KD bilateral	None	25	6	dp	0.3	6	0	d (6)	na
21	m	1997	37	3290	OU (PUV)	None	36	0	None	0.21	na	0	s	CKD
22	m	1999	34	2480	OU (PUV)	None	33	0	None	0.25	na	0	s	CKD
23	m	1996	32	2460	OU (PUV)	None	Missing	2	None	0.21	5	0	s	CKD
24	m	2002	38	2200	RA bilateral	None	21	2	dp/db	1	62	0	d (1)	na
25	f	2005	40	3300	ARPKD	45 X0	Missing	0	None	0.21	na	0	s	Normal
26	m	2001	35	2500	OU (PBS)	Small bowel stenosis	17	Yes[b]	None	0.3	9	0	d (45)	na
27	m	2002	39	4100	ARPKD	None	36	0	None	0.21	na	0	s	CKD
28	m	2002	33	2600	OU (PUV)	None	29	7	dp/db/ne	0.35	7	14	s	KTX
29	m	1998	34	2800	OU (PUV)	None	32	Yes[b]	dp/db/ne	0.40	9.6	0	s	CKD
30	f	1999	32	1630	KD bilateral	None	26	0	dp	0.3	na	0	d (1)	na
31	f	2003	36	2550	ARPKD	None	33	0	dp	1	na	0	d (1)	na
32	m	2004	35	2610	KD bilateral	Joubert syndrome	Missing	0	None	Missing	na	0	s	KTX
33	m	2007	35	3200	RVT bilateral	None	Missing	12	Missing	Missing	Missing	5	s	CKD
34	m	2005	35	2250	KD bilateral	Complex syndrome	Missing	7	None	Missing	Missing	10	[c]d (1020)	na
35	m	2005	38	2760	OU (PUV)	None	Missing	0	None	0.21	na	7	s	CKD
36	m	2002	39	3510	ADPKD	Macrocephalus	30	0	None	0.3	na	0	s	Normal

[a]ADPKD, autosomal dominant polycystic kidney disease; BW, birth weight (g); DK, bilateral dysplastic kidneys; e, epinephrine; extrarenal dx, extrarenal anomalies; f, female; GA, gestational age (weeks); KTX, kidney transplantation; LH, lung hypoplasia (on CXR); m, male; pneumo, pneumothorax; PUV, posterior urethral valves; RA/KD, renal agenesis/contralateral dysplastic kidney; renal dx, renal disease; ROH, renal oligohydramnion (gestational week, first noted); vent, mechanical ventilation.
[b]Days of mechanical ventilation not known.
[c]Died after discharge.

up to 90% [13, 15] and others mainly older series [11, 12] experiencing much poorer outcome, but some of the latter compromise in part post-mortem data. Our series conducted over a comparable time period comes close to the findings of Klaassen *et al.* reporting encouraging outcome and long-term survival of ~70% [9]. Reasons for the diverse findings are manifold: first and foremost composition of the ROH cohort with regard to the type of underlying renal disease. Presence of extrarenal comorbidities is likely to worsen prognosis; however, some of these children can be treated (but not cured) and benefit from RRT (including transplant), as can be seen in our and other series. The attitude toward providing dialysis therapy to neonates is still a matter of dispute, even among paediatric nephrologists [1]. Carey *et al.* [6] were able to demonstrate that initiation of dialysis in the neonatal period is not *per se* a negative predictor. This finding could be reconfirmed in a study from Hannover where infants with congenital kidney disease demonstrated favourable outcome on RRT comparable to older children with survival rates of 75% after a mean follow-up of 2.9 years.[23]. Three of the four babies from our series in whom dialysis was withheld perhaps would receive active treatment today. If patients survive, the neonatal period residual renal function allows conservative treatment in a good proportion of patients [8, 24]. In our own series, in three of eight children, GFR stabilized over time permitting permanent discontinuation of dialysis therapy.

Last but not least, the availability of a multidisciplinary team and local modalities of respiratory support and RRT may influence decision making profoundly. Prenatal interventions like vesicoamniotic shunting had no impact on respiratory survival and survival until discharge in our analysis. The usefulness of those interventions is still a matter of debate but may affect parental reasoning [7, 9].

Clinical presentation of ROH may range from mild respiratory and renal problems to frank respiratory failure complicated by anuria and ESRF. What makes the situation in ROH quite complicated is that the renal problem and the lung development are inextricably interconnected. After 15 weeks of gestation, amniotic fluid is predominantly produced by the fetal kidneys and oligo- or anhydramnios is suspicious of kidney dysfunction. Fetal lung liquid balance and fetal breathing are considered by far the most important factors needed for normal lung development [18, 19, 25]. Amniotic fluid (AF) production is a dynamic process requiring repeated investigations. As a rule of thumb, the earlier the detection of severe reduction in amniotic fluid, the more likely is critical pulmonary hypoplasia, and the early detection of oligohydramnios has long been regarded as an indicator of poor outcome [26].

In a recent ROH series, Klaassen *et al*. [7] found that non-survivors had a significantly earlier diagnosis of ROH than survivors. Using the diagnostic median of 30 weeks as cut-off, diagnosis of ROH prior to this was associated with a higher overall mortality. These data are supported by our

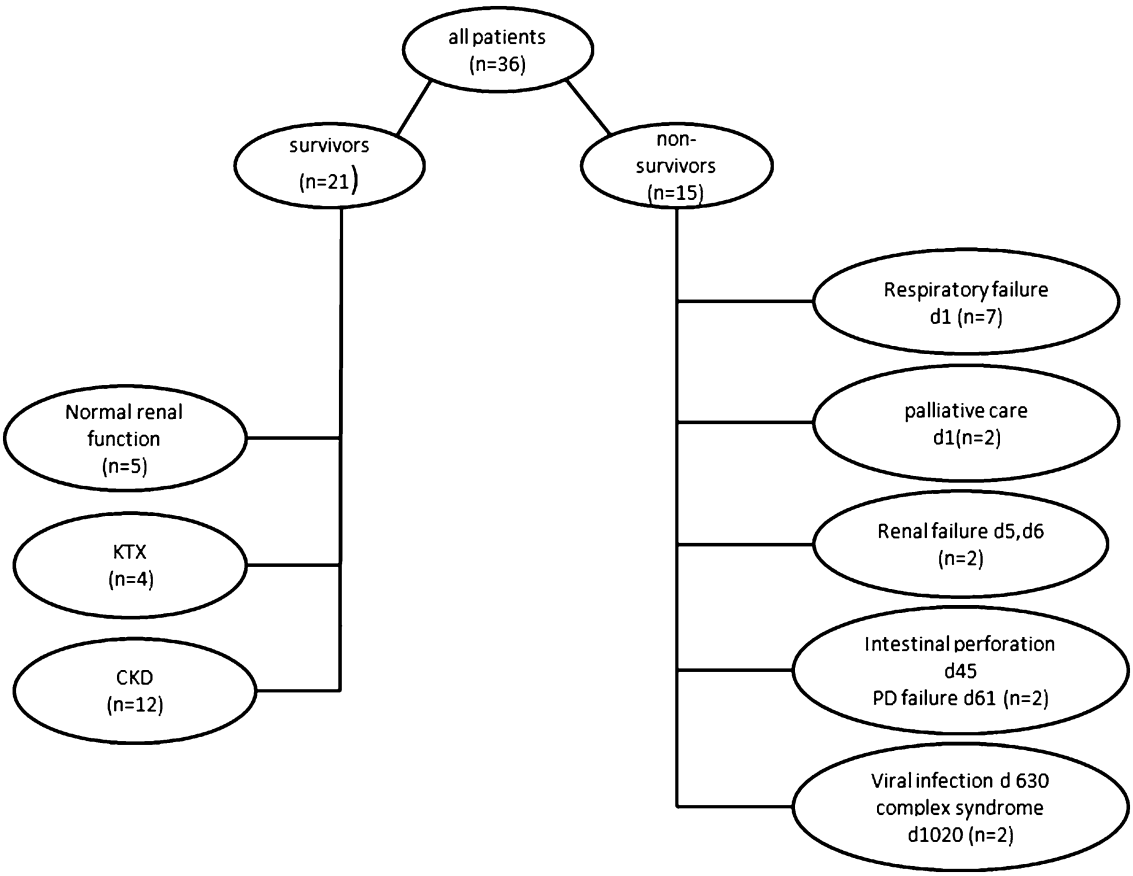

Fig. 1. Schematic representation of survival in patients with ROH.

study. Logistic regression analysis demonstrated that the risk of non-survival until discharge was increased 75-fold if ROH was diagnosed <28 weeks. In our small series, onset of ROH seems to be the best prenatal prognostic parameter to predict survival. Unfortunately, determining exact onset of ROH is somewhat problematic for obvious reasons. With detection of ROH in the third trimester, we usually do not know whether it was present before and if things have changed for the better or worse [9].

Lung growth and development are also controlled by a complex interplay of various hormonal, transcriptional and growth factors. In a transgenic model of murine renal dysgenesis. Smith *et al.* recently demonstrated that abnormal lung growth is preceded by oligohydramnios [19, 27]. This observation led them to propose the existence of a 'renal growth factor' required for adequate pulmonary development in the early embryogenesis. The distant organ effect of kidney failure to the lung has recently regained much interest in the critically ill patient under the new term kidney lung crosstalk [28, 29]. It could be hypothesized that genetic factors, growth factors and imbalance of immune/inflammatory mediators independently contribute to the

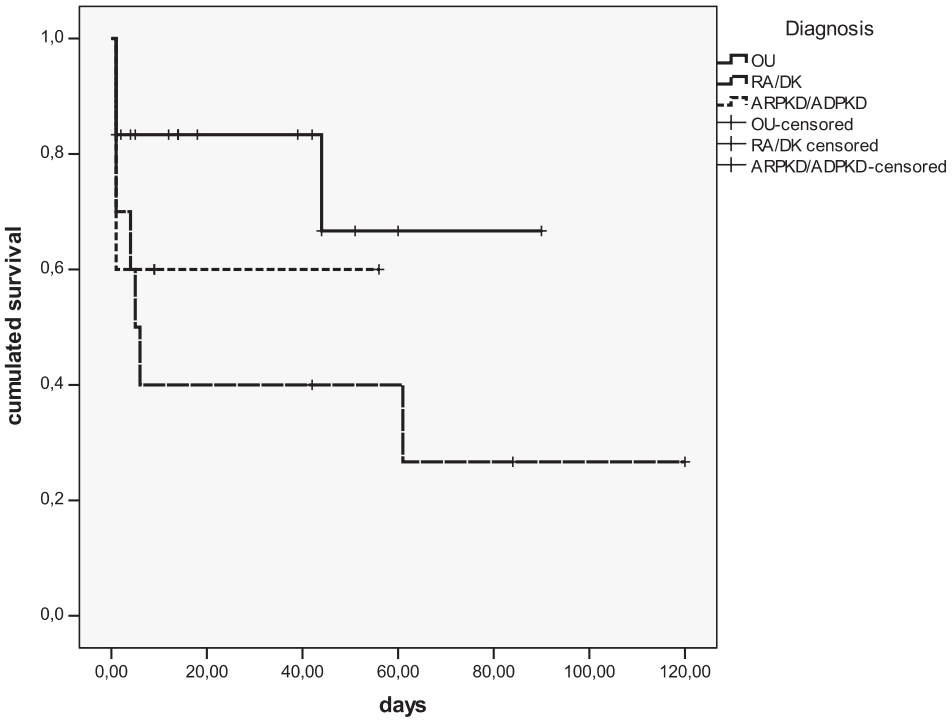

Fig. 2. Survival depending on diagnosis.

Table 2. Differences in survivors and non-survivors (survival until discharge)[a]

Survival until discharge ($n = 36$)	Survivors ($n = 23$)	Non-survivors ($n = 13$)	P-value (*t*-test, chi-square test)
Male	21 (91)	9 (69)	0.109
Female	2 (9)	4 (31)	0.109
GA (weeks)	34.7 ± 3.0	33.7 ± 2.4	0.351
Birth weight (g)	2814 ± 662	2205 ± 807	0.024
ROH first diagnosed (week)	31.6 ± 3.0	25.2 ± 5.0	<0.001
Prenatal intervention	12 (52)	9 (69)	0.513
Ventilation	12 (52)	11 (85)	0.054
Ventilation (d)	4.3 ± 5.9	5.2 ± 10.7	0.766
Pulmonary hypoplasia	10 (43)	10 (77)	0.112
Pneumothorax	5 (22)	4 (31)	0.551
OU	15 (65)	4 (31)	0.05
RA/KD	3 (13)	7 (54)	0.013
ARPKD	4 (17)	2 (15)	0.631
Associated anomalies	9 (39)	3 (23)	0.273

[a]Data presented as mean ± SD or *n* (%). GA, gestational age; OU, obstructive uropathy; RA/KD, renal agenesis/kidney dysplasia.

clinical heterogeneity of ROH. This would explain that although onset (and severity) of ROH can help predict the postnatal pulmonary course in most patients, there are some who despite early diagnosis do well and vice versa [7]. In our study, Patient no. 12 survived with normal renal function, even though ROH was diagnosed before 28 weeks, while Patient no. 5 showed ROH in Week 32 died within 24 h because respiratory stabilization was impossible. For this reason, other prognostic parameters need to be evaluated.

Prenatal assessment of lung volume has been more extensively studied in congenital diaphragmatic hernia (CDH) and claimed to be highly reliable predictor by some groups and of no use by others [30–32]. Thus, prenatal assessment of lung or AF volume may give additive information but certainly can never provide complete prognostic information (e.g. pulmonary hypertension) in ROH. In our own series, retrospective analysis of postnatal chest radiographs for lung hypoplasia did correlate poorly with early respiratory survival.

Despite some analogy to the pulmonary situation in CDH, especially in the cases where an abnormally large kidney (e.g. ARPKD) causes additional diaphragmatic compression, surprisingly little clinical data regarding respiratory outcome and management can be found in the ROH literature. If data are available, it usually describes the proportion of infants in need of ventilatory support and their complications [7, 9]. Interestingly, none of the series has tried to re-evaluate any of the prognostic

Table 3. Differences in survivors and non-survivors (survival >24 h)[a]

24 h respiratory survival ($n = 23$[b])	Survivors ($n = 16$)	Non-survivors ($n = 7$)	P-value
FiO_2 min, 1d	0.39 ± 0.21	1	<0.001
BOI, 1d	6.2 ± 2.8	43.9 ± 18.4	<0.001
CO2 min (mmHg), 1d	41.9 ± 4.2	82.7 ± 17.6	<0.001
ROH first diagnosed (week)	29.9 ± 4.9	25.4 ± 4.8	0.049
Prenatal intervention	10 (63)	5 (71)	0.701
NO	5 (31)	5 (71)	0.092
HFOV	7 (44)	6 (86)	0.089
Surfactant	11 (69)	3 (43)	0.298
Pulmonary hypoplasia	10 (63)	7 (100)	0.167
Pneumothorax	3 (19)	4 (57)	0.127

[a]Data presented as mean ± SD or *n* (%). BOI, 1d best oxygenation index at first day of life; NO, nitric oxygen.
[b]Only intubated patients requiring mechanical ventilation included; three patients died >48 h from renal failure therefore counted as survivors in this table.

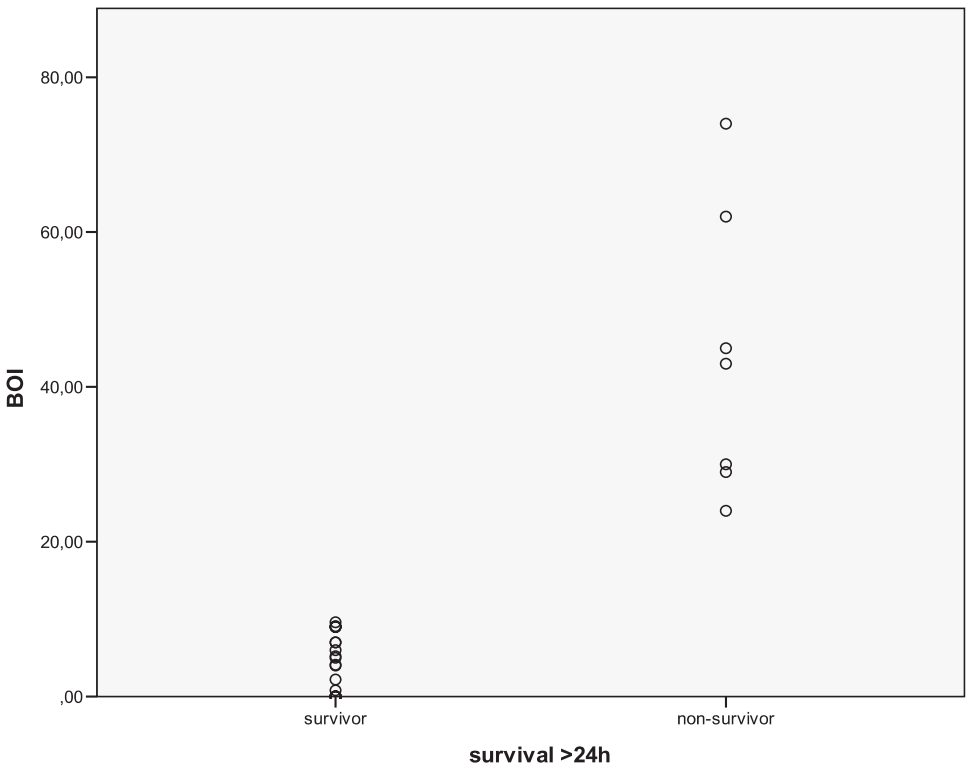

Fig. 3. BOI in survivors and non-survivors.

markers identified in CDH series [32, 33]. Our study is one of the few that gives clinical data on the pulmonary outcome in ROH. In addition to that we have attempted to assess the usefulness of the best oxygenation index (BOI) on the first day of life (1d), a predictive variable of survival in CDH in particular and in the evaluation of the need for extracorporeal membrane oxygenation in general, in the ROH setting. We found that BOI (1d) was the best postnatal prognostic parameter for prediction of the early respiratory and overall survival. BOI discriminated perfectly between survivors and non-survivors. If a BOI <10 could be achieved, no patient died from respiratory failure on the first day of life. If BOI values persisted >10, outcome was fatal within 24 h. This fact and the small sample size led to a broad range of the OR. Interestingly, our findings match well with the analysis of Sinha *et al.*, who recently published their data on prognostic indices in CDH. They identified an almost similar BOI(1d) of >11 to be the best postnatal predictor of non-survival [32]. Using logistic regression analysis for a number of potential predictors, only BOI (1d) retained significance. FiO_2 and pCO_2 also provide information, but there are limitations to both parameters (FiO_2 ceiled to 1.0; pCO_2 compromised if permissive hypercapnia is attempted) that make the composite parameter BOI probably the most robust one. Moreover, this parameter is well established in a number of lung diseases like congenital diaphragmatic hernia and meconium aspiration syndrome relevant to neonates.

This retrospective analysis has many limitations. A comparatively small number of subjects with a wide spectrum of underlying renal disorders had been studied over a long period of time. To the best of our knowledge, there had been little changes in clinical practice regarding respiratory, cardiovascular and RRT management over the study period. A paediatric peritoneal dialysis programme has been established since the early 1980s at our institution. Use of modern ventilators, surfactant, iNO and HFOV were disposable to all patients throughout the study period. The latter three variables were not significantly associated with survival in our cohort. However, retrospective studies are unable to control for subtle changes in clinical practice and unforeseen confounders.

In conclusion, BOI (1d) seems to be an available simple predictor, which can be routinely calculated. Onset of ROH $\leq/>28$ weeks may be the best predictor for survival but exact information about onset of ROH is frequently impossible to obtain for various reasons. Our finding certainly warrants reconfirmation in larger prospective studies where standardized protocols will allow reliable assessment of potential prenatal and perinatal predictors of outcome in ROH.

Conflict of interest statement. None declared.

References

1. Geary DF. Attitudes of paediatric nephrologists to management of end-stage renal disease in infants. *J Pediatr* 1998; 133: 154–165
2. Ledermann SE, Scanes ME, Fernando ON *et al.* Long-term outcome of peritoneal dialysis in infants. *J Pediatr* 2000; 136: 24–29
3. Rees L. Management of the neonate with chronic renal failure. *Semin Fetal Neonatal Med* 2008; 13: 181–188
4. Ledermann S, Rukshana S. Long-term outcome of chronic dialysis in children. *Pediatr Nephrol* 2009; 24: 463–474
5. Bunchmann TE. The ethics of infant dialysis. *Perit Dial Int* 1996; 16 (Suppl 1): 3–6
6. Carey WA, Talley LI, Sehring SA *et al.* Outcomes of dialysis initiated during the neonatal period for treatment of end-stage renal disease: a North American pediatric renal trials and collaborative studies special analysis. *Pediatrics* 2007; 119: 468–473
7. Klaassen I, Neuhaus TJ, Müller-Wiefel DE *et al.* Antenatal oligohydramnios of renal origin: long term outcome. *Nephrol Dial Transplant* 2007; 22: 432–439
8. Dillon E, Ryall AA. 10 year audit of antenatal ultrasound detection of renal disease. *Br J Radiol* 1998; 71: 497–500
9. Kemper MJ, Mueller-Wiefel DE. Prognosis of antenatally diagnosed oligohydramnios of renal origin. *Eur J Pediatr* 2007; 166: 393–398
10. Campell S, Pearce JM. Ultrasound visualization of congenital malformations. *Br Med Bull* 1983; 39: 322–331
11. Gloor JM, Ogburn PL Jr. Breckle RJ *et al.* Urinary tract abnormalities detected by prenatal ultrasound examination at Mayo Clinic Rochester. *Mayo Clin Proc* 1995; 70: 526–530
12. Rani R, Cameron A, Munro F. Prenatal diagnosis and management of urethral obstruction. *J Obstet Gynaecol Res* 1997; 23: 59–62
13. Biard JM, Johnson MP, Carr MC *et al.* Long-term outcomes in children treated by prenatal vesicoamniotic shunting for lower urinary tract obstruction. *Obstet Gynecol* 2005; 106: 503–508
14. Zaccara A, Giorandino C, Mobili L *et al.* Amniotic fluid index and fetal bladder obstruction. Do we really need more? *J Urol* 2005; 174: 1657–1660
15. El-Ghoneimi A, Desgrippes A, Luton D *et al.* Outcome of posterior urethral valves: to what extent is it improved by prenatal diagnoses? *J Urol* 1999; 162: 849–853
16. Eckoldt F, Heling KS, Woderich R *et al.* Posterior urethral valves: prenatal diagnostic signs and outcome. *Urol Int* 2004; 73: 296–301
17. Robyr R, Benachi A, Daikha-Dahmane F *et al.* Correlation between ultrasound and anatomical findings in fetuses with lower urinary tract obstruction in the first half of pregnancy. *Ultrasound Obstet Gynecol* 2005; 25: 478–482
18. Nakamara Y, Harada K, Yamamoto I *et al.* Human pulmonary hypoplasia. *Arch Pathol Lab Med* 1992; 116: 635–642
19. Joshi S, Kotecha S. Lung growth and development. *Early Hum Dev* 2007; 83: 789–794
20. Aghabiklooei A, Goodarzi P, Kariminejad MH. Lung hypoplasia and its associated major congenital abnormalities in perinatal death: an autopsy study of 850 cases. *Indian J Pediatr* 2009; 76: 1137–1140
21. Magann EF, Sanderson M, Martin JN *et al.* The amniotic fluid index, single deepest pocket, and two-diameter pocket in normal human pregnancy. *Am J Obstet Gynecol* 2000; 182: 1581–1588
22. Thibeault DW, Haney B. Lung volume, pulmonary vasculature, and factors affecting survival in congenital diaphragmatic hernia. *Pediatrics* 1998; 101: 298–295
23 Wedekin M, Ehrich JH, Offner G *et al.* Aetiology and outcome of acute and chronic renal failure in infants. *Nephrol Dial Transplant* 2008; 23: 1575–1580
24. Van Dyck M, Bilem N, Proesmans W. Conservative treatment for chronic renal failure from birth: a three year follow up study. *Pediatr Nephrol* 1999; 13: 865–859
25. Peters CA, Reid LM, Docimo S *et al.* The role of the kidney in lung growth and maturation in the setting of obstructive uropathy and oligohydramnios. *J Urol* 1991; 146: 597
26. Broshtein M, Blumenfeld Z. First- and early second-trimester oligohydramnios-a predictor of poor fetal outcome except in iatrogenic oligohydramnios pot chorionic villus biopsy. *Ultrasound Obstet Gynecol* 1991; 1: 245–249
27. Smith NP, Losty PD, Connell MG *et al.* Abnormal lung development precedes oligohydramnios in a transgenic murine model of renal dysgenesis. *J Urol* 2006; 175: 783–786
28. Bass HE, Singer E. Pulmonary changes in uremia. *J Am Med Assoc* 1950; 144: 819–823

29. Ko GJ, Rabb H, Hassoun HT. Kidney Lung crosstalk in the critically ill patient. *Blood Purif* 2009; 28: 75–83
30. Holt P, Arkovitz M, Berdon W *et al.* Newborns with diaphragmatic hernia: initial chest radiograph does not have a role in predicting clinical outcome. *Pediatr Radiol* 2004; 34: 462–464
31. Arkovitz M, Russo M, Devine P *et al.* Fetal lung head ratio is not related to outcome for antenatal diagnosed congenital diaphragmatic hernia. *J Pediatr Surg* 2007; 42: 107–110
32. Sinha CK, Islam S, Patel S *et al.* Congenital diaphragmatic hernia: prognostic indices in the fetal endoluminal tracheal occlusion era. *J Pediatr Surg* 2009; 44: 312–316
33. Chou HC, Tang JR, Lai HS *et al.* Prognostic indicators of survival in infants with congenital diaphragmatic hernia. *J Formos Med Assoc* 2001; 100: 173–175

Received for publication: 18.10.10; Accepted in revised form: 17.1.11