Antenatal oligohydramnios of renal origin: long-term outcome

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Abstract

Background. Prognosis of fetuses with renal oligohydramnios (ROH) is often still regarded as poor. Neonatal complications and the long-term follow-up of fetuses with ROH in two pediatric centres are described.

Method. 23 fetuses (16 males, 7 females) were included as patients. Primary diseases included congenital anomalies of the kidney and urinary tract (n = 16), autosomal recessive polycystic kidney disease (n = 4) and renal tubular dysgenesis (n = 3). The analysis includes retrospective chart review.

Results. Seven children died (30%), the majority (n = 4, 17%) within the neonatal period due to pulmonary hypoplasia and renal insufficiency. Fourteen patients (61%) required postnatal mechanical ventilation for a median of 4 (range 1–60) days; 11 infants had an associated pneumothorax. All 16 surviving children have chronic kidney disease (CKD) at a current median age of 5.7 years (range 0.5–14.5), managed conservatively in eight patients [median glomerular filtration rate 51 (range 20–78) ml/min/1.73 m²]. Eight patients reached end-stage renal disease at a median age of 0.3 years (range 2 days to 8.3 years), including one patient with pre-emptive kidney transplantation. Five of the patients requiring dialysis underwent successful renal transplantation at a median age of 3.5 years (range 2.5–4). Growth was impaired in seven children requiring growth hormone treatment. Cognitive and motor development was normal in 12 (75%) of the 16 patients and showed a delay in four children, including two with associated syndromal features.

Conclusion. ROH is not always associated with a poor prognosis and long-term outcome in survivors is encouraging. The high incidence of neonatal complications and long-term morbidity due to CKD requires a multidisciplinary management of these children.
with ROH that have been followed in our centres since 1990. This included a detailed analysis of (i) neonatal pulmonary and renal course, (ii) long-term renal outcome as well as (iii) extrarenal morbidity (growth and development).

Patients and methods

A total of 23 infants (16 males, 7 females) with an antenatal diagnosis of ROH that were followed in our centres after birth were included. Data were analysed retrospectively by chart review. Fourteen infants were delivered in our institutions and nine were referred from regional hospitals, all for further treatment of renal disease. Patients were diagnosed between 1990 and 2005. Twelve were followed at the University of Hamburg Children’s Hospital (center 1) and 11 at the Children’s Hospital of the University of Zurich (center 2). Median gestational age was 37 weeks (range 34–40 weeks). Patient details are presented in Table 1.

Oligohydramnios was defined as the generalized decrease in amniotic fluid. The vertical × horizontal diameter of the largest pocket was less than 2 × 1 cm² in ultrasound investigation [12,13]. The oligohydramnios was detected at a median of 30 weeks gestation (range 14–37) in 21 cases: four in the second and 17 in the third trimester. In two pregnancies, diagnosis of ROH was established immediately prior to birth due to poor maternal compliance with routine antenatal obstetrical visits.

Most children (n = 16) had CAKUT: eight infants had posterior urethral valves with associated renal dysplasia, five had bilateral renal dysplasia including one patient with VACTERL association, one patient had bilateral multicystic dysplastic kidneys and two patients had prune-belly syndrome with associated renal anomalies. In addition, four patients had autosomal recessive polycystic kidney disease (ARPKD) and three siblings had renal tubular dysgenesis.

For comparison of parametrical variables the Mann–Whitney U-test was used and for survival analysis the log-rank test (Mantel Cox) were computed using SPSS 13.0. A $P < 0.05$ was considered to be statistically significant.

Results

Mortality

Of the 23 patients seven died (30%; Figure 1 and Table 1). Four patients (17%) died in the neonatal period due to pulmonary hypoplasia and terminal renal insufficiency. None of these infants was dialysed. Three patients died later: one patient with additional multiple cardiac anomalies due to cardiomyopathy at 3.5 months, one patient with associated VACTERL anomalies due to pulmonary hypertension and renal insufficiency at the age of 5 months and one patient with ARPKD due to sepsis at the age of 14.5 months.

Non-survivors had a significantly earlier diagnosis of ROH than survivors (median 25 weeks, range 14–35 vs 31, 19–37; $P < 0.05$). Of four fetuses with ROH diagnosed in the second trimester, two died compared with 5/17 fetuses diagnosed in the third trimester. Using the diagnostic median of 30 weeks as cutoff, diagnosis of ROH prior to this was associated with a higher overall mortality (6 of 10) than diagnosis after 30 weeks gestation (1 of 11; $P < 0.02$; Figure 2). Also, neonatal mortality was more frequent in fetuses with a diagnosis prior to 30 weeks (4/10 vs 0/11, $P < 0.03$).

Neonatal course

Pulmonary outcome. Fourteen neonates (61%), including six of the seven non-survivors required artificial ventilation for a median of 4 (range 1–60) days, including one child with nasal continuous positive airway pressure (CPAP). Four neonates with antenataly suspected pulmonary hypoplasia did not need ventilation. Pneumothorax occurred in 11 infants, including one patient that did not require respiratory support.

Renal outcome. Neonatal renal dysfunction occurred in 20 of 23 children (87%). Most frequently, electrolyte imbalances and metabolic acidosis (n = 14) were present. Hypertension was diagnosed in the neonatal period in two infants with ARPKD. Severe renal dysfunction occurred in eight patients, including three of the non-survivors, who were not dialysed (patients 2-4).

Four patients (all survivors) required peritoneal dialysis in the neonatal period; however, only two for the first postnatal weeks. The other two patients started dialysis at day 3 and 4, respectively, and continued renal replacement therapy without major problems until renal transplantation (RT). One surviving patient with severe renal dysfunction suffered from superimposed pre-renal failure, that could be managed conservatively.

Long-term course

Long-term renal outcome and morbidity (Figure 3). The surviving 16 children have a current median age of 5.7 (range 0.5–14.5) years. All developed CKD, which was managed conservatively in eight patients (50%), with a median glomerular filtration rate (GFR) of 51 ml/min/1.73 m² (range 20–78).

Eight of 16 patients (50%) required renal replacement therapy at a median age of 0.3 years (range 2 days to 8.3 years); seven were started on peritoneal dialysis; however, two later switched to haemodialysis. One patient underwent pre-emptive kidney transplantation (KT) at age 8 years. Five of the children requiring dialysis received a successful renal graft at a median age of 3.5 years (range 2.7–4). Early diagnosis of ROH did not predict the risk of ESRD.
Table 1. Individual patient data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Renal and extrarenal diagnosis</th>
<th>First diagnosis of ROH (GW)</th>
<th>Gestation (weeks)</th>
<th>Mechanical ventilation (days)</th>
<th>Pneumothorax</th>
<th>Neonatal pulmonary and renal problems and outcome</th>
<th>Renal follow-up</th>
<th>Development and growth; duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>PUV</td>
<td>18</td>
<td>39</td>
<td>No</td>
<td>No</td>
<td>Respiratory failure, died in delivery room</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td>PUV, bilateral renal dysplasia</td>
<td>28</td>
<td>38</td>
<td>Yes (28)</td>
<td>Yes</td>
<td>ESRD (no dialysis), Died after 4 weeks (HMD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>f</td>
<td>Tubular dysgenesis, sister of 16</td>
<td>25</td>
<td>35</td>
<td>Yes (4)</td>
<td>Yes</td>
<td>ESRD (no dialysis) and respiratory failure, died after 4 days (HMD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>f</td>
<td>Tubular dysgenesis, sister of 16</td>
<td>26</td>
<td>34</td>
<td>Yes (2)</td>
<td>Yes</td>
<td>ESRD (no dialysis) and respiratory failure, died after 2 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>f</td>
<td>ARPKD</td>
<td>29</td>
<td>35</td>
<td>Yes (7)</td>
<td>Yes</td>
<td>Ventilation, no renal problems</td>
<td></td>
<td>Hypertension, cardiomyopathy, CKD, died after 14.5 months (pseudomonas sepsis)</td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>ARPKD, Multiple cardiac anomalies</td>
<td>35</td>
<td>39</td>
<td>No</td>
<td>No</td>
<td>CKD</td>
<td></td>
<td>Died after 3.5 months due to CKD and cardiomyopathy</td>
</tr>
<tr>
<td>7</td>
<td>m</td>
<td>VACTERL-association with bilateral renal dysplasia</td>
<td>14</td>
<td>34</td>
<td>No</td>
<td>No</td>
<td>Colostomy, pulmonary hypertension</td>
<td></td>
<td>Died after 5 months of CKD and pulmonary hypertension</td>
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<td>8</td>
<td>m</td>
<td>Bilateral renal dysplasia</td>
<td>33 (amniotic infusion)</td>
<td>40</td>
<td>No</td>
<td>No</td>
<td>CKD, Acidosis</td>
<td></td>
<td>ESRD, PD started age 8.3, switched to HD age 8.7</td>
</tr>
<tr>
<td>9</td>
<td>m</td>
<td>ARPKD</td>
<td>32</td>
<td>37</td>
<td>Nasal CPAP (1)</td>
<td>No</td>
<td>CKD, Hypertension</td>
<td></td>
<td>GFR 20 ml/min/1.73 m²</td>
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<tr>
<td>10</td>
<td>f</td>
<td>Bilateral renal dysplasia</td>
<td>28</td>
<td>38</td>
<td>Yes (22)</td>
<td>No</td>
<td>ESRD, PD since day 4</td>
<td></td>
<td>Height SDS -0.59, 7.5 years</td>
</tr>
<tr>
<td>11</td>
<td>m</td>
<td>PUV, bilateral renal dysplasia</td>
<td>20</td>
<td>37</td>
<td>Yes (5)</td>
<td>Yes</td>
<td>acute pre-renal failure, feeding problems</td>
<td></td>
<td>GH age 1.5-2.9, Height SDS -2.4, 6.1 years</td>
</tr>
<tr>
<td>12</td>
<td>f</td>
<td>Bilateral renal dysplasia, Syndromal features</td>
<td>36</td>
<td>40</td>
<td>No</td>
<td>No</td>
<td>CKD</td>
<td></td>
<td>Development delay, GH age 1.0 to KT, Height SDS -2.65, 6.1 years</td>
</tr>
</tbody>
</table>

GH since age 3.9, Height SDS -1.59, 11.8 years
<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Antenatal</th>
<th>Postnatal</th>
<th>Treatment/Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>m</td>
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<td>19 (amniotic infusion)</td>
<td>35</td>
<td>Yes (5) No CKD</td>
</tr>
<tr>
<td>14</td>
<td>m</td>
<td>PUV, Trisomy 21 syndrome</td>
<td>unknown</td>
<td>36</td>
<td>No No CKD, recurrent pyelonephritis</td>
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<td>15</td>
<td>m</td>
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<td>34</td>
<td>35</td>
<td>No Yes CKD</td>
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<tr>
<td>16</td>
<td>m</td>
<td>PUV, bilateral renal dysplasia</td>
<td>33</td>
<td>37</td>
<td>Yes (7) Yes CKD</td>
</tr>
<tr>
<td>17</td>
<td>f</td>
<td>Multicystic renal dysplasia</td>
<td>unknown</td>
<td>40</td>
<td>Yes (4) No ESRD, PD started day 3</td>
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<tr>
<td>18</td>
<td>m</td>
<td>PUV, VUR</td>
<td>32</td>
<td>34</td>
<td>Yes (60) Yes Acute renal failure, PD for 21 day, small-bowel-perforation, myocardial infarction, sepsis</td>
</tr>
<tr>
<td>19</td>
<td>m</td>
<td>PUV, bilateral renal dysplasia</td>
<td>37</td>
<td>38</td>
<td>Yes (3) Yes CKD</td>
</tr>
<tr>
<td>20</td>
<td>m</td>
<td>Bilateral renal dysplasia, vesico-ureteral reflux</td>
<td>36</td>
<td>40</td>
<td>No No CKD</td>
</tr>
<tr>
<td>21</td>
<td>m</td>
<td>ARPKD</td>
<td>30</td>
<td>36</td>
<td>Yes (1) Yes CKD, Hypertension</td>
</tr>
<tr>
<td>22</td>
<td>f</td>
<td>Tubular dysgenesis</td>
<td>28</td>
<td>38</td>
<td>Yes (26) Yes Acute renal failure, PD for 4 weeks</td>
</tr>
<tr>
<td>23</td>
<td>m</td>
<td>PUV, bilateral renal dysplasia</td>
<td>32</td>
<td>34</td>
<td>No No CKD, maximum. serum creatinine 3.1 mg/dl</td>
</tr>
</tbody>
</table>

ARPKD, autosomal recessive polycystic kidney disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; GH, growth hormone; HMD, hyaline membrane disease; KT, kidney transplantation; ROH, oligohydramnios of renal origin; PD, peritoneal dialysis; PUV, posterior urethral valves; VUR, vesico ureteric reflux; GFR, glomerular filtration rate.
Extrarenal morbidity

Growth. Current median height of the 16 children is \(-1.59\) standard deviation (SDS) (range \(-2.9\) to \(+0.9\)); (Figure 4). Seven patients required treatment with recombinant growth hormone (GH) for a median period of 3.5 years (range 1.5–7.2), which was discontinued at the time of renal transplantation. One patient on haemodialysis still receives GH. Two patients with SDS \(<-2\) currently show catch-up growth after RT.

Development. Gross cognitive and motor development is normal in 12 of 16 patients (75%). They have normal motor function and attend normal schools (primary school: \(n=3\), secondary school: \(n=3\), kindergarten; \(n=4\), excluding two patients younger than 3 years).

Developmental delay is present in four children. One patient with concomitant birth asphyxia (patient 11) developed spastic quadriplegia (legs more than arms) with minor cognitive deficits, but attended kindergarten. One girl (patient 12) with associated congenital muscular hypotonia, clubfeet and dysmorphic facial features has moderately delayed motor and speech development but attends kindergarten. One patient (patient 14) has Down’s syndrome, with associated developmental delay and muscular hypotonia. One patient after a protracted neonatal course and long-term ventilation and multiple complications (patient 18) has muscular hypotonia and feeding problems.
Discussion

This report indicates that not all fetuses with ROH have a poor outcome. Although neonatal mortality and morbidity are significant, multidisciplinary efforts can result in an encouraging long-term prognosis. Although all surviving patients have CKD, sometimes requiring renal replacement therapy from the first days of life, the majority of patients can be managed conservatively.

Very few data on early neonatal outcome of ROH are available. One reason for this might be the fact that termination of pregnancy is still frequently practised for fetuses with ROH [6]. In contrast, one recent study documented a survival of 91% for male patients with ROH, lower urinary tract obstruction and vesicoamniotic shunting [14]. No precise data, however, on neonatal and long-term morbidity were stated in this publication. In a study from Zaccara et al. [15], 12 of 18 patients with an intrauterine diagnosis of bladder outlet obstruction and ROH could be followed-up after birth; of these, three died due to pulmonary hypoplasia compared with none in a group without ROH.

Our study for the first time presents detailed data on the neonatal clinical course after ROH, extending a previous limited experience in 10 patients [16]. Pulmonary complications due to pulmonary
anomalies. Future efforts should also focus on with developmental delay had associated congenital appropriate for age in most patients. Two children evaluated prospectively and in precise detail, is objective assess fetal renal function non-invasively of severe renal disease [7]. Unfortunately, efforts to conservatively for a long time, despite antenatal evidence proportion of these patients can be managed con-

Whether antepartum amnioinfusion is a way to prevent or ameliorate pulmonary hypoplasia in neonates is a matter of debate. Experimental evidence is in favour and supported by recent studies; however, prospective data for ROH are lacking [9,18–20]. Two patients in our series received amnioinfusion treatment, but the series is too small to allow conclusions. Also, the value of antenatal surgery in ROH due to obstructive uropathies to improve pulmonary (and renal) function is under debate and is currently viewed with caution [21].

In the neonatal period, only a minority of patients in our series actually needed dialysis, comparing data of infants with other causes of neonatal renal failure [22]. Neonatal renal dysfunction, electrolyte disorders or hypertension, however, were present in almost all patients. Thus, nephrological expertise is necessary for optimal treatment. In addition, some patients required urological interventions, again underlying the multi-
disciplinary approach, including diagnostic imaging facilities and genetic expertise. The latter is demonstrated by the heterogeneous postnatal course in a family with three fetuses suffering from renal tubular dysgenesis [23]. Whether more aggressive treatment of renal insufficiency (e.g. dialysis in all patients with severe renal dysfunction), further improves outcome, cannot be concluded from our data.

The long-term outcome is mainly influenced by the degree of CKD. Although care of infants with CKD is a challenge, recent reports demonstrate a good prognosis so that treatment is recommended [24]; this notion is also supported by our results. A large proportion of these patients can be managed conservatively for a long time, despite antenatal evidence of severe renal disease [7]. Unfortunately, efforts to objectively assess fetal renal function non-invasively and accurately remains unsatisfactory [25].

Extrarenal morbidity includes growth retardation, which can be managed successfully by optimized nutrition, growth hormone and erythropoietin treatment and RT. Neurological outcome, though not evaluated prospectively and in precise detail, is appropriate for age in most patients. Two children with developmental delay had associated congenital anomalies. Future efforts should also focus on elimination of additional risk factors for developmental delay, such as perinatal asphyxia present in one of our patients. However, our data clearly indicate that renal dysfunction in a patient without asphyxia is not a risk factor for adverse neurological outcome, although neonates with asphyxia often have renal dysfunction [3].

Of the potential risk factors discussed, early diagnosis of ROH, i.e. occurrence in the first and second trimester, has been regarded an indicator of poor outcome [26] but not unanimously [13]. In some series, patients with cardiac malformations and termination of pregnancies were included. In our series, patients with poor overall survival had a significantly earlier diagnosis; however, this has to be viewed with caution, since early diagnosis is not able to differentiate between poor and good outcome. Individual patients with a very early diagnosis did well and vice versa some patients with late (or delayed) diagnosis died or had poor renal outcome. Mortality after the neonatal period, e.g. due to sepsis and heart disease is not always and necessarily related to ROH. Furthermore, interindividual fetal diagnostic accuracy as well as patient compliance with antenatal routine visits will remain a problem and results may not always be reliable. Nevertheless, early presentation of ROH must be viewed critically and future studies should prospectively address the predictive value of antenatal sonographical tools, e.g. time of diagnosis and other indices of severity.

The present observation is limited by the selected patient group, limited sample size and the retrospective analysis. Only fetuses followed in our tertiary pediatric nephrology centres were included, thus excluding fetuses not surviving intrauterine life due to intrauterine death or termination of pregnancy. Nevertheless, we believe that our conclusions are valid, since all infants with postnatal care were included, indicating that an overall negative prognosis for fetuses with ROH is not justified. This has important consequences for antenatal and genetic counseling. Our data confirm the obligation to implement a clinic for antenatal counseling for fetuses with CAKUT and renal disorders. Especially if ROH is present, the multidisciplinary approach has to be established before birth, including a neonatologist and pediatric nephrologists. Counseling of affected families should aim at neutral, balanced information to parents with individu-
dualized, independent decisions according to the family situation.

In summary and conclusion, our data indicate that the majority of fetuses with ROH have an encouraging long-term prognosis if a multidisciplinary approach is available [27]. Future efforts should include improved antenatal detection of risk factors and interdisciplinary antenatal counseling. If a decision is made to deliver the fetus, referral to a tertiary neonatal and pediatric nephrology centre seems mandatory.

Conflict of interest statement. None declared.
References


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