Prenatal diagnosis of urinary tract anomalies, a cohort study in the Northern Netherlands

Short running title: Prenatal diagnosis of urinary tract anomalies

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What is already known about this topic?

- Urinary tract (UT) anomalies are among the most frequent congenital anomalies.

What does this study add?

- After the introduction of the prenatal screening program an increase in prevalence of anomalies of the collecting system was observed.
- Due to the high uptake of the second trimester anomaly scan and improved skills of the sonographers, more UT anomalies are detected prenatally that would otherwise remain undetected, because of no or limited clinical consequences.

Abstract

Objective: To describe prevalence, time of diagnosis and type of birth in children and fetuses with urinary tract (UT) anomalies after the introduction of the anomaly scan in the Netherlands in 2007.

Methods: We selected, from a population-based congenital anomaly registry, children and fetuses with UT anomalies born between 2008-2014. Cases were defined according to type of UT anomaly and whether isolated or with associated anomalies. Information was collected on time of diagnosis and type of birth.

Results: We included 487 cases. Total prevalence increased from 34.0 in 2008 to 42.3 per 10,000 births in 2014, mainly by an increase in anomalies of the collecting system. Almost 70% presented as isolated. Anomalies of the renal parenchyma were more often associated with genetic or other anomalies (47.3%) than anomalies of the collecting system (19.0%). The proportion of prenatally diagnosed cases increased from 59.3 % in 2008 to 80.9% in 2014. Termination of pregnancy occurred in 14.8%, of which the majority were UT anomalies associated with a genetic disorder or other anomalies.

Conclusion: In the period after the introduction of the anomaly scan we observed an increasing prevalence of anomalies of the collecting system, but no increase in termination of pregnancies.
Introduction

Renal urinary tract (UT) anomalies are among the most common congenital anomalies. The average European prevalence was 32.8/10,000 births over the period 2010-2014. UT anomalies represent a broad phenotypic spectrum, ranging from renal agenesis, cystic kidney diseases, hydronephrosis and lower urinary tract obstructions, all with a wide range in severity. Some anomalies are incompatible with life, such as bilateral renal agenesis, while other anomalies are mild and may remain undetected if not diagnosed by ultrasound. Risk factors for UT anomalies include genetic and non-genetic factors, such as maternal obesity and fertility treatment, whereas the use of folic acid is reported to reduce the risk. UT anomalies are more commonly observed in male fetuses. Because congenital UT anomalies are the cause of 30 to 40 percent of cases of end-stage renal disease, especially in young children, early diagnosis is important to start therapy and minimize renal damage.

Before the introduction of the prenatal screening program in the Netherlands in 2007, ultrasound scans were only performed on clinical indication (suspected poor or excessive fetal growth, including oligo- or polyhydramnios, positive family history for congenital anomalies, use of teratogens, diabetes etc.) or for keepsake. In 2007, a national prenatal screening program was introduced in the Netherlands, including the combined first trimester screening for trisomy 21, 13 and 18 and an anomaly scan between 18-22 weeks of gestation. The latter is offered free of charge to all pregnant women with an uptake of more than 90%. When an anomaly is suspected, the pregnant woman is referred to a Fetal Medicine Unit, a tertiary center for prenatal diagnosis where an advanced ultrasound scan is performed by a specialist and, if appropriate, additional genetic testing is offered.

The aim of this study was to examine whether in the period after the introduction of the prenatal screening program there were specific trends in the prevalence of UT anomalies, clinical presentation, time of diagnosis and outcome of pregnancies in which the fetus was affected with an anomaly of the urinary tract.

Methods

We conducted a study within Eurocat Northern Netherlands, a population-based congenital anomaly registry covering the three Northern provinces of the Netherlands (approximately 10% of all births in the Netherlands). Cases are identified by active case ascertainment, using multiple sources including hospital files, prenatal diagnosis reports and post mortem reports. Cases are registered in the database after parental consent. For cases with a delivery date in 2010 and beyond, basic
information is registered (anomalies, type of birth, time of diagnosis), if parents do not answer to a second request for consent. Information on these so called ‘non-responders’ is registered to be able to calculate prevalence rates. There is no lower gestational age limit for registration, so early terminations for fetal anomalies and fetal deaths are included. The upper age limit for inclusion is 10 years. Cases are coded using the ICD10-BPA classification system\(^9\) by trained registry staff.

We selected from the database cases with a major anomaly of the urinary tract (ICD10 code within range Q60-Q64) and with an end of pregnancy date (birth, miscarriage or termination of pregnancy) between January 1, 2008 and December 31, 2014.

Since there are many different types of anomalies of the urinary tract, we categorized cases into 4 groups: malformations of the renal parenchyma, anomalies of the urinary collecting system, abnormal embryonic migration of kidneys and other UT anomalies and combinations of UT anomalies (table 1).\(^{10}\) The categorization was based on the primary UT anomaly. If a child had for instance renal dysplasia developing as consequence of an obstruction, the anomaly was classified as obstruction and categorized under ‘anomalies of the urinary collecting system’.

[insert table 1 here]

For each case we included information on sex, clinical presentation (isolated, part of a genetic condition or syndrome, or associated with multiple congenital anomalies (MCA)), time point the UT anomaly was detected (prenatally versus postnatally), and the status at birth (live birth (LB), still birth (SB), spontaneous abortion (SA), termination of pregnancy for fetal anomaly (TOP)).

Analyses were performed in IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY: IBM Corp.). Differences between UT anomaly categories were examined using the \(X^2\) test. Trends in prevalence were examined for the period 2010-2014 which included the ‘non-responders’, using the \(X^2\) test for trend. Trends in prenatal detection and birth types were examined for the whole period (2008-2010) since the denominator is all UT anomalies registered in the Eurocat database and the non-response should not be biased to certain UT anomalies. A p-value <0.05 was considered to be statistically significant. This study was done with anonymised patient data and therefore ethics committee approval was not necessary.
Results

Between 2008 and 2014, 119,297 births were monitored in the Eurocat Northern Netherlands region and 487 fetuses and children were registered with a major anomaly of the urinary tract. The majority of these cases had an anomaly of the collecting system (n=302, 62.0%), whereas only 27.7% (n=135) had an anomaly of the renal parenchyma. In the supplementary table the specific anomalies per category are presented. The majority of cases were in male fetuses (n=330, 67.8%). The total prevalence was 40.8 per 10,000 births and increased from 34.0 per 10,000 births in 2008 to 42.3 per 10,000 births in 2014 (Figure 1). This increase was mainly attributable to anomalies of the collecting system which increased from 19.5 to 29.9 per 10,000 births in the same period. Trend analyses over the period 2010-2014 (which included the ‘non-responders’) showed a non-significant increase for all UT anomalies (p=0.062) and a significant increase in anomalies of the collecting system (p=0.048). There was no such trend observed for the other types of UT anomalies.

Most UT anomalies presented as isolated, 69.6% (n=339). Whereas 16.4% (n=80) presented as part of a known genetic condition or syndrome, 14.0% (n=68) were associated with other major anomalies. Most frequent genetic conditions, associations or syndromes included VACTERL/VATER (n=8), Meckel-Gruber (n=7), trisomy 18 (n=7), limb body wall complex (n=6), Omphalocele-Estrophy-Imperforate Anus – Spinal defects complex (OEIS complex; n=5), autosomal dominant polycystic kidney disease (n=3), trisomy 21 (n=3) and Turner syndrome (n=3). Anomalies of the collecting system presented most frequently as isolated (247/302, 81.8%), whereas 37.0% (10/27) of the cases with a combination of UT anomalies had a genetic background or were part of a syndrome.

In total, 72.3% (n=352) of the UT anomalies were detected prenatally, with an increase from 59.3% in 2008 to 80.9% in 2014 (X² for trend p<0.001, figure 2). The prenatal detection of anomalies of the renal parenchyma was 76.1% over the total period and fluctuated between 60.0% (in 2014) and 90.0% (in 2010) (X² for trend p=0.581, figure 2). Prenatal detection of cases with an anomaly of the collecting system was 70.4% over the study period and increased from 55.9% in 2008 to 81.3% in 2014 (X² for trend p<0.001, figure 2). For specific UT anomalies of the renal parenchyma and collecting system the prenatal detection varied between 0% for epispadias to over 90% for multicystic dysplastic kidney, ureteropelvic junction stenosis, stenosis of urethra or bladder neck and absence of bladder and urethra (Supplementary table). The prenatal detection rates for migration anomalies and multiple anomalies were 65% and 85% respectively over the total period.

[insert figure 1 here]

[insert figure 2 here]
There was a significant difference in prenatal detection according to the different clinical presentations of UT anomalies. The proportion of prenatally detected UT anomalies was highest among cases presenting as isolated UT anomalies (79.9%, n=270). Of the UT anomalies that were part of a syndrome or genetic condition or of MCA prenatal detection occurred in 62.5% (n=50) and 47.1% (n=32), respectively (p<0.001). The timing of prenatal detection varied according to the different UT categories. Over the total period, 17% (n=59) of the prenatally detected UT anomalies were detected after 22 weeks gestation, these were mainly anomalies of the collecting system (n=46).

The vast majority of fetuses with a UT anomaly were live births, 81.9% (n=399). Terminations of pregnancy and intra-uterine deaths occurred in 14.8% (n=72) and 3.3% (n=16), respectively. No trend in status at birth was observed over the study period. The latter however differed by clinical presentation and UT category (Table 2). In isolated UT anomalies or UT anomalies associated with a genetic condition or syndrome, live births occurred in 92.6% and 55.0%, respectively. The highest proportion of pregnancy terminations was observed in UT anomalies associated with a genetic condition or syndrome (41.3%). Since anomalies of the collecting system present most frequently as isolated, 91.4% of the cases with an anomaly of the collecting system were live born, while in cases with multiple UT anomalies fetal deaths (14.8%) and terminations of pregnancy (33.3%) were more frequent.

[insert table 2 here]

**Discussion**

This study is the first to report on the prenatal diagnosis of UT anomalies after the introduction of a prenatal screening program. The results show an increasing trend in the proportion of prenatally detected UT anomalies, in particular for anomalies of the collecting system, between 2008-2014. The majority of fetuses with an UT anomaly are live births; termination of pregnancy is chosen mainly when the UT anomaly is part of a genetic condition or syndrome or when it is part of a more severe spectrum (more than 1 type of UT anomaly present).

We observed a non-significant increase in prevalence of UT anomalies of any kind and a significant increase in anomalies of the collecting system. The prevalence of UT anomalies in our study is higher than the European prevalence of 32.8 per 10,000 births reported in the EUROCAT network over 2010-2014. There is a significant variation in prevalence of UT anomalies among (European) regions, with prevalence rates ranging between 12 and 71 per 10,000 births. Several non-genetic risk factors,
such as maternal diabetes, obesity and subfertility\textsuperscript{3,4,11} have been identified that may explain in part the variations and trends that are observed in prevalence of (specific types of) UT anomalies. It remains unclear whether folic acid has a protective effect\textsuperscript{5} or increases the risk\textsuperscript{4} for (specific) urinary tract anomalies.

Other studies have found that the prevalence of UT anomalies was affected by the availability of prenatal screening and ultrasound services. An increase in kidney anomalies, observed in Denmark between 2007 and 2012, was most likely due to an increase in completeness of registration and an improved (prenatal) diagnosis because of better diagnostic sensitivity of ultrasound.\textsuperscript{12} Garne et al. found in an European cohort study on hydronephrosis, that the availability of prenatal screening services was related to the variability in prevalence. If there was no standard prenatal screening, the prevalence of congenital hydronephrosis was in general lower.\textsuperscript{13}

The increasing prevalence in anomalies of the collecting system in our study is most likely also the result of improved prenatal diagnosis due to the high uptake of the second trimester anomaly scan and improved skills of the sonographers. The prenatal screening program was swiftly introduced in 2007 and many sonographers were trained at that time to perform the anomaly scan. The uptake of the anomaly scan was over 90\% during the study period and did not increase in a substantial way. During the anomaly scan, a complete fetal anatomy survey is carried out, including the urinary system. The sonographer investigates the bladder (size, filling), presence of both kidneys, echogenicity of renal parenchyma and diameter of the pyela. As a consequence, a large majority of the UT anomalies are detected prenatally, except for anomalies that are difficult to visualize on US such as epispadias, vesico-uretero-renal reflux and posterior valves. Detection on US of enlarged pyela or hydronephrosis may have led to an improved prenatal diagnosis of the underlying primary obstructive UT anomaly. In the period before the introduction of the prenatal screening program (2000-2006), the prevalence of UT anomalies was much lower in the Northern Netherlands (24.6 per 10,000 births) compared to the prevalence thereafter (40.8 per 10,000 births in 2008-2014).\textsuperscript{14} The higher prevalence rate found in this study supports the conclusion that the anomaly scan has led to more UT anomaly diagnoses.

Although the prenatal detection rate increased during the study period to over 80\%, no increase in termination of pregnancies was observed in our cohort. Our results are in line with other studies that documented high prenatal detection rates and relatively low termination rates. In a European study on multicystic dysplastic kidney (MCDK) in children born between 1997-2006, the prenatal detection rate was 88\%. The choice for TOP was associated with the severity of MCDK, with higher rates in bilaterally affected cases or when associated anomalies were present. The authors
concluded that good prenatal detection can potentially inflate the prevalence rates, since some MCDK cases may involute postnatally, making a postnatal diagnosis impossible.\textsuperscript{15}

The decision of a couple to terminate the pregnancy depends greatly on the long-term prognosis. In some instances, during the course of the pregnancy, the findings on ultrasound may normalize and the child may have an excellent prognosis. In a prospective cohort of 115 patients with prenatally diagnosed UT anomalies, in particular children with a prenatal isolated unilateral or bilateral hydronephrosis had a favorable outcome. Oligohydramnios and postnatal bilateral anomalies are risk factors for unfavorable outcome (such as need for surgery or persistent renal anomalies with impaired renal function).\textsuperscript{16} In another study on 284 fetuses affected with a lower urinary tract obstruction and delivered between 1995-2007 in the West Midlands (England) a prenatal diagnosis rate of 51\% was observed in all cases and somewhat higher in complex cases, compared to isolated cases. TOP was performed in 41\% of complex cases and in 19\% of isolated cases.\textsuperscript{17} These proportions are comparable with our study where TOP was chosen in 41\% of cases with a genetic condition or syndrome diagnosis and 33\% of the MCA cases. In general, TOP is associated with more severe types of UT anomalies.

Anomalies of the collecting system represented the largest group in our study. This group includes primary hydronephrosis, which is a common obstructive anomaly, but also one of the UT anomalies that may have a favorable prognosis. In a recent study in one Dutch hospital, 24\% of the children who were prenatally diagnosed with hydronephrosis were not confirmed postnatally or had mild dilatation without clinical consequences and only 19\% developed complications (recurrent UT infections or pyelonephritis).\textsuperscript{18}

We performed a population-based cohort study, using data from a high quality registry for congenital anomalies. For each case there was detailed information available on UT- and possible additional anomalies, coded by trained registry staff. When performed, information from genetic tests was available. Therefore, we were able to classify the cases very precisely according to clinical presentation. Another strength is that we had detailed information on the time of detection and type of birth for each case. Since Eurocat only collects data on fetuses and infants with an anomaly, we were not able to include fetuses where an UT anomaly was suspected prenatally, but had resolved during pregnancy. However, it was not the aim of our study to evaluate the prognosis and outcome of prenatally detected UT anomalies. The registry uses multiple sources for case-finding. Although the registry tries to capture all the cases with a congenital (UT) anomaly, the registration may not be complete, due to non-consent of the parents. Approximately 7\% of the parents do not
give consent for registration. Also, it may take some time to capture all the cases through active case-finding. Therefore, the most recent years may be less complete.

In conclusion, after the introduction of the prenatal screening program we observed a non-significantly increased prevalence of all UT anomalies and a significant increase in the prevalence of anomalies of the collecting system. Currently over 80% of the UT anomalies are detected prenatally. Some of these anomalies might have remained undetected without anomaly scan, because of no or limited clinical consequences and may cause (unnecessary) anxiety for the future parents. Although more UT anomalies were prenatally diagnosed, no increase in termination of pregnancies was observed. It is important to improve information on follow-up of children prenatally diagnosed with UT anomalies to provide parents with correct information on the long-term prognosis.

References


(14) EUROCAT Website Database. Number of cases, prevalence per 10,000 births and proportion of Urinary, for the following registries: N Netherlands (NL), from 2000 - 2006. 07/04/2017; Available at: http://www.eurocat-network.eu/accessprevalencedata/prevalencetables. Accessed 08/03, 2017.


Figure 1  Total annual prevalence of urinary tract anomalies per 10,000 births, for all UT anomalies and per category, between 2008 and 2014 in the Northern Netherlands.
Figure 2: Prenatal detection of urinary tract anomalies in the Northern Netherlands between 2008 and 2014, for all UT anomalies and for anomalies of the renal parenchyma and anomalies of the collecting system.
Table 1 Categorization of urinary tract anomalies according to the primary UT anomaly.

<table>
<thead>
<tr>
<th>Category</th>
<th>UT anomalies included</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Malformations of the renal parenchyma</td>
<td>renal agenesis, renal hypoplasia, multicystic dysplastic kidney, cystic kidney, polycystic kidney, renal dysplasia, dysplastic kidney in Meckel Gruber syndrome</td>
</tr>
<tr>
<td>II Anomalies of the urinary collecting system</td>
<td>hydronephrosis (end stage of obstructive anomalies), ureteropelvic junction stenosis, megaloureter, hydroureter, duplication of ureter, vesico-uretero-renal reflux, epispadias, exstrophy of urinary bladder, OEIS complex, (posterior) urethral valves, stenosis, atresia of urethra and bladder neck, absence of bladder and urethra</td>
</tr>
<tr>
<td>III Abnormal embryonic migration of kidneys and other UT anomalies</td>
<td>pelvic kidney, horse shoe kidney, other malformations of urinary system</td>
</tr>
<tr>
<td>IV Combination of UT anomalies</td>
<td>Presence of at least two types of UT anomalies, both considered to be primary anomalies and belonging to at least two categories</td>
</tr>
</tbody>
</table>

Abbreviations: UT=urinary tract, OEIS= omphalocele-exstrophy-imperforate anus-spinal defects
<table>
<thead>
<tr>
<th>Category of UT anomaly</th>
<th>Live births</th>
<th></th>
<th>Fetal deaths</th>
<th></th>
<th>Termination of pregnancy for fetal anomaly</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>anomalies of renal parenchym</td>
<td>94</td>
<td>69.6%</td>
<td>4</td>
<td>3.0%</td>
<td>37</td>
<td>27.4%</td>
</tr>
<tr>
<td>anomalies of collecting system</td>
<td>276</td>
<td>91.4%</td>
<td>6</td>
<td>2.0%</td>
<td>20</td>
<td>6.6%</td>
</tr>
<tr>
<td>anomalies of renal migration and other</td>
<td>15</td>
<td>65.2%</td>
<td>2</td>
<td>8.7%</td>
<td>6</td>
<td>26.1%</td>
</tr>
<tr>
<td>multiple renal anomalies</td>
<td>14</td>
<td>51.9%</td>
<td>4</td>
<td>14.8%</td>
<td>9</td>
<td>33.3%</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>isolated</td>
<td>314</td>
<td>92.6%</td>
<td>6</td>
<td>1.8%</td>
<td>19</td>
<td>5.6%</td>
</tr>
<tr>
<td>genetic/syndromic/sequence</td>
<td>44</td>
<td>55.0%</td>
<td>3</td>
<td>3.8%</td>
<td>33</td>
<td>41.3%</td>
</tr>
<tr>
<td>MCA</td>
<td>41</td>
<td>60.3%</td>
<td>7</td>
<td>10.3%</td>
<td>20</td>
<td>29.4%</td>
</tr>
<tr>
<td>Total</td>
<td>399</td>
<td>81.9%</td>
<td>16</td>
<td>3.3%</td>
<td>72</td>
<td>14.8%</td>
</tr>
</tbody>
</table>

Abbreviations: UT=urinary tract, MCA=multiple congenital anomalies