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Antenatal diagnosis and management of fetal megacystis and lower urinary tract obstruction
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Fetal Megacystis: prediction of spontaneous resolution and outcome

Fontanella F., Duin L., Adama van Scheltema PN, Cohen-Overbeek TE, Pajkrt E, Bekker M, Willekes C, Bax CJ, Bilardo CM.
Abstract

Objectives: To investigate the natural history of fetal megacystis from diagnosis in utero to postnatal outcome, and to identify prognostic indicators of spontaneous resolution and postnatal outcome after resolution.

Methods: This was a national retrospective cohort study. Fetal megacystis was defined in the first trimester as a longitudinal bladder diameter (LBD) ≥ 7 mm, and in the second and third trimesters as an enlarged bladder failing to empty during the entire extended ultrasound examination. LBD and gestational age (GA) at resolution were investigated with respect to likelihood of resolution and postnatal outcome, respectively. Sensitivity, specificity and area under the receiver–operating characteristics curve (AUC) were calculated.

Results: In total, 284 cases of fetal megacystis (93 early megacystis, identified before the 18th week, and 191 late megacystis, identified at or after the 18th week) were available for analysis. Spontaneous resolution occurred before birth in 58 (20%) cases. In cases with early megacystis, LBD was predictive of the likelihood of spontaneous resolution (sensitivity, 80%; specificity, 79%; AUC, 0.84), and, in the whole population, GA at regression was predictive of postnatal outcome, with an optimal cut-off at 23 weeks (sensitivity, 100%; specificity, 82%; AUC, 0.91). In the group with early megacystis, the outcome was invariably good when resolution occurred before the 23rd week of gestation, whereas urological sequelae requiring postnatal surgery were diagnosed in 3/8 (38%) cases with resolution after 23 weeks. In the group with late megacystis, spontaneous resolution was associated with urological complications after birth, ranging from mild postnatal hydronephrosis in infants with resolution before 23 weeks, to more severe urological anomalies requiring postnatal surgery in those with resolution later in pregnancy. This supports the hypothesis that an early resolution of megacystis is often related to a paraphysiological bladder enlargement that resolves early in pregnancy without consequences, while antenatal resolution occurring later in pregnancy (after the 23rd week of gestation) should suggest a pathological condition with urological sequelae.

Conclusions: In fetal megacystis, LBD and GA at regression can be used as predictors of resolution and outcome, respectively. These parameters could help in fine-tuning the prognosis and optimizing the frequency of follow-up scans.
Introduction

Fetal megacystis is detected at the first-trimester ultrasound examination in about 1 in 1500 pregnancies (1). The fetal bladder can appear enlarged due to obstructive or non-obstructive causes (2). In the first case, a bladder outlet obstruction (or lower urinary tract obstruction (LUTO)) results in increased intraluminal pressure along the urinary tract, with hydronephrosis and increased echogenicity of the renal parenchyma, along with oligohydramnios from the second trimester onwards (3). This condition is associated with high perinatal mortality and poor postnatal renal function (4). Non-obstructive causes include a heterogeneous group of conditions with no evidence of obstruction, such as the rare megacystis-microcolon-intestinal hypoperistalsis syndrome (2-5). Not all cases of megacystis show progression with advancing gestation and previous studies have even reported cases of spontaneous resolution during pregnancy (Table 1). Owing to the variable etiology, evolution and prognosis, prenatal counseling in fetal megacystis is challenging (6).

Previous studies have analyzed the likelihood of spontaneous resolution exclusively in cases of megacystis identified during the first trimester, reporting that longitudinal bladder diameter (LBD) at diagnosis can be used to guide the prenatal diagnostic work-up and predict the prognosis (7-9). However, information on the natural history and the prediction of resolution and postnatal outcome after antenatal resolution of megacystis, in particular in cases diagnosed later in pregnancy, is limited.

The aim of this study, therefore, was to investigate the natural history of fetal megacystis from diagnosis in utero to postnatal outcome, and to identify prognostic indicators of spontaneous resolution and postnatal outcome after resolution.

Table 1. Spontaneous resolution of fetal megacystis reported in the literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Postnatal diagnosis</th>
<th>( n )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early resolution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liao (2003)(7)</td>
<td>No urological sequelae</td>
<td>71</td>
</tr>
<tr>
<td>Nijagal (2004)(19)</td>
<td>No urological sequelae</td>
<td>1</td>
</tr>
<tr>
<td>Sebire (1996)(1)</td>
<td>No urological sequelae ( (n = 6) ); postnatal hydronephrosis ( (n = 1) )</td>
<td>7</td>
</tr>
<tr>
<td><strong>Late resolution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confer (2010)(16)</td>
<td>Anterior urethral valves</td>
<td>1</td>
</tr>
<tr>
<td>Montemarano (1998)(20)</td>
<td>Non-refluxing non-obstructive megacystis-megaureter</td>
<td>1</td>
</tr>
<tr>
<td>Müller-Brochut (2014)(18)</td>
<td>No urological sequelae ( (n = 1) ); associated congenital anomalies ( (n = 1) )</td>
<td>2</td>
</tr>
<tr>
<td>Jouannic (2003)(17)†</td>
<td>Partial PUV ( (n = 1) ); partial PUV + associated congenital anomalies ( (n = 1) )</td>
<td>2</td>
</tr>
</tbody>
</table>

Only first author of each study is given.*Studies with no information on postnatal outcome were excluded; bladder dimension was not mentioned in most studies.†No information on gestational age at resolution was available. PUV, posterior urethral valves.
Methods

This was a national retrospective multicenter study carried out at the Fetal Medicine Units (FMUs) of the eight University Medical Centers in the Netherlands. The time span of data collected from each database was dependent on the period during which data had been stored in the database. This was from January 2000 to the end of 2014 in three centers (Erasmus Medical Center, Rotterdam; Academic Medical Center, Amsterdam; University Medical Center, Maastricht), from January 2004 to the end of 2014 in two centers (University Medical Center, Groningen; Radboud University Medical Center, Nijmegen) and between January 2007 and the end of 2014 in the remaining centers (Leiden University Medical Center, Leiden; Utrecht University Medical Center, Utrecht; Vrije University Medical Center, Amsterdam). These FMUs act as referral centers for all anomalies suspected in peripheral hospitals and external ultrasound clinics in The Netherlands. Fetal megacystis was defined between the 10th and 14th weeks of gestation as LBD ≥ 7 mm, and in the second and third trimesters as an enlarged bladder failing to empty during an extended ultrasound examination lasting at least 40 min. Cases referred either after the routine second-trimester scan or after scans performed later in pregnancy for growth or other obstetric indications were defined as late megacystis, whereas all cases referred before 18 weeks were defined as early megacystis.

Prenatal and postnatal data were collected in all cases. Measurements of LBD at referral, anteroposterior renal pelvic diameter and ureteral enlargement throughout the pregnancy were retrieved from the local databases in 85% of the cases (n = 240), and in the remaining 15% (n = 44) measurements were performed (by F.F.) on suitable images stored in the database with the built-in measurement tool. For subsequent analysis, cases which had been treated with antenatal bladder drainage and terminations of pregnancy were excluded. In continuing pregnancies, the degree of bladder enlargement, together with that of renal pelvis and ureters, was monitored throughout pregnancy by scans performed at regular intervals. Pyelectasis was defined as an anteroposterior renal pelvic diameter ≥ 4 mm or ≥ 7 mm, during the second or third trimester of pregnancy, respectively (10). The megacystis was considered to be resolved if the bladder was observed to be empty following fetal micturition.

For liveborn infants, we collected information on gestational age (GA) at birth, birth weight and final diagnosis, as well as data on postnatal management, surgery and medical examinations. Estimated glomerular filtration rate was calculated using the Schwartz formula (11), using the infant’s length and the creatinine nadir within the first year of diagnosis.

Groups were compared using the chi-square test for categorical variables and independent samples t-test for continuous variables. Receiver–operating characteristics (ROC) curve analysis was used to evaluate the predictive accuracy of LBD and GA at
resolution in predicting the likelihood of resolution and postnatal outcome, respectively. All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA) and MedCalc (MedCalc, Mariakerke, Belgium) software.

**Results**

We identified from the databases 541 cases of fetal megacystis. Of these, 257 (47.5%) were excluded (Figure 1; Table 2). The natural history, from diagnosis *in utero* to postnatal outcome, was reviewed in the remaining 284 pregnancies, which included 93 cases of early megacystis (referred before the 18th week) and 191 cases of late megacystis (referred ≥ 18th week). Spontaneous resolution occurred before birth in 58 (20%) cases: in 35 (38%) cases of early and in 23 (12%) cases of late megacystis.

LBD was a good predictor of resolution (area under the ROC curve (AUC), 0.84; Figure 2) for the group with early megacystis, referred before the 18th week, while its reliability was poor when megacystis was diagnosed at or beyond this gestational age (AUC, 0.67; Table 3). Of the 93 cases with early megacystis, 40 had LBD ≤ 12 mm, of which 70% (n = 28) resolved antenatally, and 53 cases had LBD > 12 mm, of which 13% (n = 7) resolved antenatally.

Six infants had no information available for the postnatal period, having been lost to follow-up (Table 4). Overall, after birth, in 33/52 (63%) cases there were no major urological abnormalities found, while 19/52 (37%) infants presented a urological anomaly requiring surgical correction.

GA at spontaneous resolution was a good predictor of the need for urological surgery after birth, with an AUC of 0.91 and an optimal cut-off point at 23 weeks (Figure 3). As shown in Table 5, GA at resolution was accurate in predicting the outcome of the total population, and also separately in the early and the late megacystis groups.

Of the 93 early megacystis cases, antenatal resolution occurred in 35 (38%): in 27 cases before 23 weeks and in eight cases later in pregnancy (Figure 1). Of the 27 cases with resolution before the 23rd week, four were lost to follow-up and the remaining 23 infants did not require any surgical intervention after birth. Conversely, of the eight cases with late resolution, urological surgery was required in 38% (n = 3).
Figure 1: Flowchart summarizing study population of cases of fetal megacystis, indicating numbers with spontaneous resolution and subsequent outcome. LBD, longitudinal bladder diameter; TOP, termination of pregnancy.
Table 2. Overview of the study population derived from 541 cases of megacystis diagnosed prenatally in The Netherlands

<table>
<thead>
<tr>
<th></th>
<th>GA at diagnosis (weeks)</th>
<th>LBD (mm)</th>
<th>Associated anomalies (% (n))</th>
<th>Liveborn (% (n))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excluded</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOP (n = 188)</td>
<td>15 (11–25)</td>
<td>33 ± 20</td>
<td>43 (80/188)</td>
<td>—</td>
</tr>
<tr>
<td>Antenatal intervention (n = 40)</td>
<td>20 (12–30)</td>
<td>43 ± 20</td>
<td>0 (0/40)</td>
<td>38 (15/40)</td>
</tr>
<tr>
<td>Lost to follow-up (n = 29)</td>
<td>19 (12–24)</td>
<td>30 ± 24</td>
<td>21 (6/29)</td>
<td>—</td>
</tr>
<tr>
<td>Eligible for inclusion (n = 284)</td>
<td>22 (11–36)</td>
<td>35 ± 22</td>
<td>29 (83/284)</td>
<td>77 (218/284)</td>
</tr>
<tr>
<td>Early megacystis (n = 93)</td>
<td>13 (11–17)</td>
<td>18 ± 12</td>
<td>32 (30/93)</td>
<td>60 (56/93)</td>
</tr>
<tr>
<td>Resolution (n = 35)</td>
<td>13 (11–17)</td>
<td>12 ± 6</td>
<td>20 (7/35)</td>
<td>100 (35/35)</td>
</tr>
</tbody>
</table>

Data are given as median (range), mean ± SD or % (n). GA, gestational age; LBD, longitudinal bladder diameter; TOP, termination of pregnancy.

Of the 191 late megacystis cases, spontaneous resolution occurred in 23 (12%): in four cases before 23 weeks and in 19 cases later in pregnancy. Two infants were lost to follow-up, one with early and one with late resolution. Of the remaining 18 cases with antenatal resolution after 23 weeks, urological surgery was required in 89% (n = 16) (including 10 male infants with LUTO and evidence of residual posterior urethral valves at postnatal cystoscopy). Conversely, among the three cases with resolution before the 23rd week which were followed up, no infant presented urological sequelae requiring surgery (only mild pyelectasis was diagnosed at postnatal investigation in two infants).

Another prenatal predictor of outcome was the prenatal finding of pyelectasis or dilated ureters at follow-up scan after resolution of bladder enlargement. In fact, this was observed in all fetuses with postnatal evidence of vesicoureteral reflux (VUR), and in 25% of the remaining cases.

Figure 2: Receiver–operating characteristics curve of longitudinal bladder diameter for prediction of antenatal resolution in early megacystis (n = 93). Diagonal segments produced by ties. Area under the curve, 0.84.
Figure 3. Receiver–operating characteristics curve of gestational age at resolution of megacystis for prediction of need for urological surgery after birth in entire cohort \((n = 284)\). Diagonal segments produced by ties. Area under the curve, 0.91.

Table 3. Prediction of resolution: performance of longitudinal bladder diameter (LBD) in the prediction of spontaneous resolution in cases of early or late prenatal diagnosis of megacystis and in the entire cohort

<table>
<thead>
<tr>
<th>LBD cut-off</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>LR+</th>
<th>LR−</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort ((n = 284))</td>
<td>22 mm</td>
<td>73</td>
<td>83</td>
<td>4.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Early megacystis ((n = 93))</td>
<td>12 mm</td>
<td>80</td>
<td>79</td>
<td>3.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Late megacystis ((n = 191))</td>
<td>22 mm</td>
<td>65</td>
<td>83</td>
<td>3.8</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 4. Infant characteristics and outcome according to gestational age at resolution of fetal megacystis

<table>
<thead>
<tr>
<th>Resolution</th>
<th>All ((n = 58))</th>
<th>&lt; 23 weeks ((n = 31))</th>
<th>≥ 23 weeks ((n = 27))</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated ultrasound anomalies</td>
<td>26 (15/58)</td>
<td>23 (7/31)</td>
<td>30 (8/27)</td>
<td>NS</td>
</tr>
<tr>
<td>No major urological sequelae</td>
<td>63 (33/52)</td>
<td>100 (26/26)</td>
<td>27 (7/26)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Urological sequelae requiring surgery</td>
<td>37 (19/52)</td>
<td>0 (0/26)</td>
<td>73 (19/26)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mean eGFR (mL/min/1.73 m²)</td>
<td>98</td>
<td>104</td>
<td>82</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Data are given as % \((n)\) unless otherwise stated. Five cases resolving < 23 weeks and one case resolving ≥ 23 weeks were lost to postnatal follow-up.* For difference between resolution < 23 or ≥ 23 weeks of gestation. eGFR, estimated glomerular filtration rate; NS, not significant.
Table 5. Prediction of outcome: performance of gestational age (GA) at resolution in the prediction of postnatal urological surgery for bladder enlargement in cases of early or late prenatal diagnosis of megacystis and in the entire cohort

<table>
<thead>
<tr>
<th>GA cut-off</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>LR+</th>
<th>LR−</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort (n = 284)</td>
<td>23 weeks</td>
<td>100</td>
<td>82</td>
<td>5.6</td>
<td>0</td>
</tr>
<tr>
<td>Early megacystis (n = 93)</td>
<td>23 weeks</td>
<td>100</td>
<td>67</td>
<td>3.0</td>
<td>0</td>
</tr>
<tr>
<td>Late megacystis (n = 191)</td>
<td>24 weeks</td>
<td>100</td>
<td>84</td>
<td>6.3</td>
<td>0</td>
</tr>
</tbody>
</table>

AUC, area under the receiver–operating characteristics curve; LR+/-, positive/negative likelihood ratio.

Discussion

This is the largest study to date on the natural history of fetal megacystis detected at any trimester during pregnancy. We report on the antenatal evolution of 284 cases of early or late diagnosis of megacystis, and on the postnatal outcome of 58 cases which resolved antenatally. Our study shows that LBD is a reliable predictor of spontaneous resolution, particularly of early megacystis, and that GA at resolution is a good predictor of postnatal outcome. From our study it can be inferred that the ideal LBD cut-off associated with antenatal resolution in early megacystis is 12 mm and the critical GA cut-off for an uneventful resolution is 23 weeks.

LBD at the first-trimester scan has been analyzed previously in relation to the risk of chromosomal defects or progression of megacystis. Liao et al. (7) found that about 90% of cases of megacystis with normal karyotype and LBD ≤ 15 mm resolved spontaneously, with all resolving cases presenting LBD ≤ 12 mm. Our study confirms that LBD can indeed be used to inform on the likelihood of spontaneous resolution. Furthermore, the cut-off of 12 mm has been reported in the literature as a method to define cases with moderate first-trimester megacystis (LBD between 12 and 15 mm) (11). Over the last few decades, fetal therapy before 18 or even before 16 weeks, in the form of fetal vesicoamniotic shunt and fetal cystoscopy, has been attempted with the aim of preventing early renal damage. Ruano et al. (11), studying the feasibility of early cystoscopy, considered not eligible for fetal therapy any case with moderate megacystis (LBD, 12–15 mm), performing early fetal cystoscopy only in cases with LBD > 15 mm. Our study confirms that it would be appropriate to exclude from therapy cases with LBD ≤ 12 mm, as in 70% of these cases the bladder enlargement resolved spontaneously.

An interesting finding of this study is the difference in outcome after a diagnosis of megacystis, depending on the timing of resolution, with a worse prognosis in the case of late resolution. In fact, most of the cases resolving at or after the 23rd week required urological surgery after birth, whereas all infants with antenatal resolution before 23 weeks
had a good outcome without major urological sequelae. This finding cannot be compared with those of other published studies as information about resolution is confined to small studies without systematic reporting of postnatal outcome and GA at regression (Table 1).

Thus, in the case of early megacystis the prognosis is good and without urological sequelae if resolution occurs before 23 weeks, whereas major urological sequelae cannot be ruled out in the case of late resolution. The excellent prognosis for infants with early resolution of early megacystis supports the hypothesis of a temporary paraphysiological dilatation of the fetal bladder during the first stages of life, as suggested by Liao et al. (7). In fact, autonomic innervation of the bladder and smooth muscle fibers appear only after the 13th week of gestation (12). Therefore, the finding of a dilated bladder before this period can be transient and without any pathological anatomical basis. Conversely, in the case of late megacystis, surgery for LUTO or other urological anomalies was required after birth in 89% of cases with antenatal resolution after the 23rd week of gestation, while no urological sequelae, with the exception of mild pyelectasis postnatally, were recorded in cases with antenatal resolution before 23 weeks.

At follow-up ultrasound examination, even in the presence of apparent fetal micturition, the renal pelvis or ureters remained dilated in all fetuses with postnatal evidence of VUR. Previous studies (13, 14) have shown that a reduction in diameter of a previously enlarged fetal bladder in association with concomitant renal pelvic enlargement does not necessarily indicate ‘micturition,’ but rather VUR. In view of these findings, we recommend always including measurements of the renal pelvis both when the bladder appears enlarged and also after resolution. For this purpose, the hydronephrosis index, defined by Leung et al. (15) as the ratio of antero-posterior pelvic diameter/urinary bladder volume, may be helpful in discriminating cases at risk of urological sequelae.

A strength of this study, compared with other large studies in the literature, is that we had data covering at least 6 months of follow-up. Moreover, our follow-up was based mainly on medical reports rather than patient questionnaires, which may reflect only partially the true clinical picture.

An important limitation of our study is that for all cases of late megacystis no information regarding earlier scans was available. This means that we can only assume, and cannot be sure, that the megacystis was late in onset. This also implies that early megacystis cases with spontaneous resolution before the second-trimester scan are not included in the study and the rate of early spontaneous resolution may therefore have been underestimated. Another limitation of this study, and of the other studies investigating second- and third-trimester megacystis, is that there is still no agreement as to which cut-off defines a pathologically enlarged bladder. Previous retrospective studies followed the subjective criteria of a bladder failing to empty over a period of at least 45 min (8, 9). Owing to the retrospective nature of this study, we could not apply this definition, and relied upon the description of fetal
megacystis on the medical reports of extended ultrasound examinations lasting at least 40 min. Further studies are therefore needed in order to establish an objective definition of fetal megacystis during the second and third trimesters.

In conclusion, when faced with a case of early megacystis, the LBD can assist in predicting the chance of resolution, and the outcome will be favorable if resolution occurs before the 23rd week. This applies also to megacystis diagnosed later in pregnancy, as resolution beyond 23 weeks does not exclude urological sequelae. These findings should be of help in informing parents and in deciding upon the optimal medical management of this condition.
References


Part 2

Antenatal diagnosis and management of LUTO