

Evaluation of Fetuses Diagnosed with Megacystis During Prenatal Period

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ABSTRACT

OBJECTIVES: Fetal megacystis is very rare; however this problem may be associated with other structural or chromosomal abnormalities leading to morbidity and mortality. Due to renal injury and pulmonary hypoplasia, the prognosis is poor especially in fetuses with early-onset oligohydramnios. In this study, we evaluated the management strategies and outcomes of fetal megacystis in our hospital.

STUDY DESIGN: The data of cases who were prenatally diagnosed with megacystis between 1 January 2017 and 31 December 2019 were analyzed. Ultrasonography findings and antenatal interventions were withdrawn from the computerized database. Information about postpartum status was also received. The data were analyzed in terms of diagnostic methods, fetal interventions (vesicosynthesis, vesicoamniotic shunt), potential prognostic markers and short/long-term outcomes.

RESULTS: A total of 15 megacystis patients were detected. One of the fetuses was female and the remaining cases were male. Six of the patients were isolated. Ten patients underwent invasive procedures for prenatal aneuploidy diagnosis and one of them diagnosed with trisomy 18. Totally, 4 patients underwent vesicosynthesis; however, no vesicoamniotic shunt was recorded. Four fetuses were terminated and intrauterine fetal demise occurred in 2 fetuses. Four patients were lost during follow up. Survival rate was 33.3%.

CONCLUSION: Fetal megacystis is an important ultrasonographic finding which may be a component of chromosomal/genetic anomalies. This problem may also be isolated in some cases. Because of the poor outcome, parents should be well informed and all interventions should be offered to families.

Keywords: Chromosomal abnormality, Megacystis, Oligohydramnios, Posterior urethral valve, Prenatal diagnosis

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Introduction

Fetal urine production begins at approximately 10th weeks of gestation. The fetal bladder can easily be visualized as a round or oval structure without echogenicity between two umbilical arteries in the pelvis by routine ultrasonography (1). Although urogenital anomalies are common, megacystis (MC) is very rare and its incidence is reported to be 0.06% (2,3). It has been reported that several genetic, environmental and teratogens may be responsible for urinary tract abnormalities (4). However, etiological factors directly related to MC has not been clarified yet.

The longitudinal diameter of the normal bladder in the first trimester is usually <6mm (2). The diagnosis of early-onset MC is made when the bladder is detected more than 7mm in the first-trimester ultrasonography. In the second and third trimesters, there is not a definitive cut-off value for the MC diagnosis, but the diagnosis is commonly made by the persistence of at dilated bladder visualization (1). MC is 8 times

more frequent in male fetuses compared to female fetuses (4). MC pathogenesis is divided into two subgroups as obstructive and non-obstructive. Main non-obstructive causes are Prune Belly syndrome (PBS), Megacystis Microcolon Intestinal Hypoperistaltism Syndrome (MMIHS), chromosomal anomalies (especially trisomy 13 and 18), primary mega urethra, vesicoureteral reflux (VUR) and neurogenic megacystis. On the other hand, obstructive causes are more common and posterior urethral valve (PUV), urethral atresia and urethral stricture are the main causes in this group (5).

When the reasons of MC were examined one by one, the most common cause is shown to be lower urinary tract obstruction secondary to PUV (57%) (6). PUV is seen in 1/8 000 - 1/25 000 births and is responsible for %4 of perinatal deaths. The presence of classical keyhole and thickened bladder wall may be detected in PUV related MC with an antenatal ultrasound examination (4). MC may be associated with a chromosomal abnormality in %15 of cases, especially in the non-obstructive group. An increase in nuchal translucency (NT) may be detected in patients with concurrent chromosomal abnormalities (6).

Gestational week at diagnosis, severity and type of obstruction effect postnatal prognosis. The prognosis varies according to the underlying pathology. Isolated obstructive MC can be treated in the prenatal period with several interventions. Methods such as vesicoamniotic shunt (VAS), valve resection and urinary stent are used for treatment in the literature (6,7)

We evaluated the characteristics, follow-up processes, postnatal course and clinical management of fetuses who were diagnosed with MC in our perinatology clinic.

Material and Method

This study was designed retrospectively. The study protocol was approved by the Local Committee of Ethics in our hospital (90057706-799) and conducted according to the Declaration of Helsinki. Signed informed consent could not be obtained for the present study because of the retrospective design. Patients who were admitted to Ankara Etlik Zubeyde Hanim Woman's Health Care, Training and Research Hospital and diagnosed with megacystis between 1 January 2017 and 31 December 2019 were included in the study. Fetal bladder longitudinal diameter was measured between the bladder dome and the bladder neck in a sagittal plane, and the longest distance was used to diagnose MC. Diagnosis of fetal MC was made if the bladder size was >7mm in the first trimester. If the bladder was dilated in two sonographic evaluations within 45 minutes in the second and third trimester, fetuses were accepted to have MC. Patients diagnosed with MC were evaluated in perinatology council and detailed fetal ultrasonographic examination was performed for each case. Then, the appropriate invasive procedure was offered to determine both karyotype analysis and renal functions. The renal

function was evaluated by using the laboratory findings of beta 2-microglobulin, osmolality, sodium, chlorine, calcium and total protein in the fetal urine sample.

Concurrent pelviectasis, echogenicity in the kidneys, urinary tract abnormalities and oligo/anhydramnios were noted. Cases without additional anomalies except urinary system anomalies were accepted as isolated MC. Patients were informed about prognosis and intrauterine treatment options after the detailed evaluation. Vesicosynthesis was performed to evaluate the renal function as a first step approach. VAS was recommended only for patients considered as isolated lower urinary tract obstruction with oligohydramnios and renal functions favoring a good prognosis. Postnatal genetic testing was recommended for patients who didn't accept prenatal karyotype examination. Informed consent was obtained for invasive procedures and archived in patient files. All prenatal diagnoses were confirmed by postnatal examination of the fetuses and postnatal images were also recorded.

All necessary data was withdrawn from the hospital registry system retrospectively. Information about the final health status of cases who did not continue to follow up was obtained by phone call.

Statistical analyses were performed using SPSS version 22 (Statistical Package for the Social Sciences, Chicago). Data were expressed as mean \pm standard deviation, median (range) and percentage.

Results

There was a total of 15 MC cases during the study period. The characteristics, prenatal and postnatal findings of the cases are shown in table I. One of the fetuses was female and the remaining cases were all male. The median maternal age was 27 years (range between 19-33). The median diameter of the fetal bladder was found to be 19.35 mm (min. 10 mm / max. 61 mm). The median gestational week at the time of MC diagnosis was 13 weeks (range between 11-33). The gestational week at the diagnosis was under 18 weeks in 13 cases; thus early-onset MC rate was found to be 86.6%.

There was one twin pregnancy in which co-twin was healthy and remaining 14 were singletons. Ten of the patients were isolated (66.6%), however, 5 were associated with other system abnormalities (33.4%). The most common concurrent anomalies were; single umbilical artery (SUA), ascites, increased intestinal echogenicity, choroid plexus cyst, extremity anomalies and increased NT. Polyhydramnios was detected in one pregnancy which was thought to be secondary to skeletal dysplasia. In remaining cases, the amniotic fluid was normal or decreased. Ten patients underwent antenatal invasive testing (66%) and 1 patient had trisomy 18, while other karyotype results were all normal.

Table 1: The characteristics, prenatal and postnatal findings of fetal megacystis cases

Case	Gestational Week	Size	Maternal Age	Prenatal invasive procedure	Ultrasonography findings at the time of diagnosis	Vesicosynthesis	Vesicoamniotic shunt	Clinical course	Postnatal evaluation	Final status
1	135/7	11 mm	30	Normal (AS)	None Dichorionic-diamniotic twin pregnancy	No	No	Double-bubble, pelviclectasis, a-s-bilical artery, bilateral dysplastic kidney in the fetus with MC. Died at week 33 ^{6/7} . 2380 gr co-twin baby boy was delivered at 35 ^{6/7} by CS with 9/10 APGAR score	No autopsy for the fetus with MC Co-twin was healthy	IUFD
2	113/7	15 mm	26	None	Single umbilical artery	No	No	Anhydramnios at 16 ^{3/7} , right multicystic dysplastic kidney and left hydronephrosis at 22 ^{3/7} , 1850 gr baby boy was delivered at 30w by CS with 2 APGAR score	Bilateral multicystic dysplastic kidney, diagnosed with PBS. Chromosomal analysis was normal. Died at 13 hours during postpartum period	PPex
3	122/7	22 mm	21	Normal (AS)	Increased intestinal echogenicity, increased echogenicity in the kidneys	No	No	Not continued follow-up	Verbally learned that the baby was healthy	Healthy
4	123/7	11 mm	21	None	Increased intestinal echogenicity, increased echogenicity in the kidneys	No	No	Not continued follow-up	Could not get information about the latest status	N/A
5	172/7	13 mm	29	None	None	No	No	Bladder size was normal, 3100 gr baby boy was delivered at 39w by CS	No problem in the postpartum period.	Healthy
6	172/7	20 mm	19	Normal (AS)	Pelviclectasis, increased intestinal echogenicity	Yes (184/7)	No (B2 microglobulin: 7.6, osmolality: 169)	Pelviclectasis, 3120 gr baby boy was delivered vaginally at 38 ^{2/7}	Neonatal examination was normal. Postpartum follow-up was normal	Healthy
7	152/7	48 mm	26	Normal (AS)	Bilateral choroid plexus cyst, unilateral pes equinovarus, thickening of the bladder wall and increased echogenicity	Yes (19w)	No (B2 microglobulin: 3.6, osmolality: 166)	Resolution after vesicosynthesis, bilateral hydronephrosis, 2800 gr baby boy was delivered at 37 ^w by CS due to anhydramnios	Bilateral hydronephrosis in the postpartum period, bladder size was normal. Diagnosed with PBS. Could not get information about the latest status	N/A
8	133/7	14 mm	29	Trisomy 18 (CVS)	Absence of nasal bone, bilateral choroid plexus cyst	No	No	Termination at 183/7	No autopsy	ToP
9	124/7	10 mm	32	Normal (CVS)	None	No	No	Bilateral hydronephrosis, no follow-up after the 24 th week	Could not get information about the latest status	N/A
10	133/7	15 mm	27	Normal (CVS)	Pelviclectasis	No	No	Anhydramnios and intrauterine fetal demise at 164/7	No autopsy	IUFD
11	291/7	36 mm	32	Normal (AS, cordocentesis, Microarray test)	Clenched hand, hook shape hand, pelviclectasis, rocker-bottom feet, hydrocephalus, polyhydramnios	No	No	2260 gr baby boy was delivered at 35 ^{7/7} by CS because of fetal distress with 3/5 Appgar score	Bilateral grade 5 hydronephrosis, hydrocephalus, clenched hand, rocker-bottom feet, and syndromic face view were detected. Died due to cardiac arrest on the 7 th day postpartum.No Autopsy	PPex
12	334/7	61 mm	21	None	None	No	No (B2-microglobulin: 8.4 mg/L; osmolality: 250 mOsm/kg)	Not continued follow-up	Could not get information about the latest status	N/A
13	13	26 mm	24	Normal (CVS)	Increased echogenicity in the kidneys	Yes (131/7)	No (B2-microglobulin: 8.4 mg/L; osmolality: 250 mOsm/kg)	Vesicosynthesis at 145/7, termination due to bad prognostic test results of renal functions	No autopsy	ToP
14	136/7	33 mm	33	Normal (CVS)	Increased echogenicity in the kidneys, increased nuchal translucency	Yes	No (Family refluxed VAS operation)	Hydrops fetalis at 194/7 (ascites in the abdomen, pericardial effusion, diffuse subcutaneous edema), 400 gr female baby terminated due to anhydramnios	No autopsy	ToP
15	165/7	31 mm	33	None	Pelviclectasis increased echogenicity in the kidneys	No	No	Terminated due to anhydramnios	No autopsy	ToP

Footnotes AS: Amniocentesis; CVS: Chorionic villus sampling; CS: Cesarean section; IUFD: Intrauterine fetal demise; PBS: Prune Belly Syndrome; PPex: Postpartum exitus; ToP: Termination of pregnancy; VAS: Vesicoamniotic shunt

Four of the patients did not continue their antenatal follow-up (26.6%), and we had sufficient postnatal information about only one of them. Four pregnancies with early-onset anhydramnios or hydrops fetalis were terminated (26%). In two patients (one co-twin), intrauterine demise occurred (13%) at 16th and 35th gestational weeks. Two of the 6 alive born fetuses died during the postpartum period. There were 4 fetuses alive at the time of study among 12 cases; thus survival rate was 33.3%.



Figure 1: Images of fetal megacystis in two fetuses at different gestational weeks. a) first trimester, b) second trimester

Discussion

Hydronephrosis, dysplastic kidney, and oligohydramnios may complicate ongoing pregnancies with fetal MC due to lower urinary tract obstruction. Voiding disorders, renal failure, growth retardation or infertility are the other important complications in surviving fetuses (5). In these cases, bladder decompression before 20 weeks of gestation is thought to reduce perinatal mortality and morbidity (6). However, it should be kept in mind that procedures such as VS and VAS are temporary solutions. Fetal cystoscopic laser ablation is also a permanent alternative to PUV treatment but it has more serious complications (ascites, fetal death) and not a widely used method yet (7). To prevent fetal mortality, it is recommended to regulate the amount of amniotic fluid before the canalicular phase is completed during lung development phases (8). Beside the intrauterine treatment modalities, families may refuse these options. In this study; only 4 of 15 (26.7%) cases underwent VS, but no VAS was performed due to the family decision.

As shown in the present study, lower urinary tract obstructions are the leading cause of MC. This problem may be a component of different genetic or syndromic disorders. However, it may also be an isolated fetal abnormality without any associated findings. Antenatal invasive procedures may be useful to evaluate the chromosomal structure and renal function of the fetus in some cases. VAS should be considered in selected cases with normal karyotype after obtaining good prognostic test results by VS (9).

Despite all these diagnostic awareness, the etiology of megacystis may not be clearly identified in some fetuses with prenatal interventions. For this reason, postnatal evaluation is also important to have more detailed information about this

issue and to provide adequate information to families. According to a systemic review, the most common abnormalities associated with fetal megacystis was reported to be increased NT, followed by SUA and cardiac anomalies (10). Increased intestinal echogenicity, echogenic kidneys, and pelvicaliectasis were the most common findings in our series. Due to the lack of information, first trimester NT measurements could not be obtained for all cases in our study. Among 5 cases with first-trimester ultrasonography reports, 1 had an increased NT.

If keyhole sign, bladder wall thickening, and echogenicity are detected with ultrasonography, PUV should be considered as the potential cause of MC. However, it should be noted that these findings are not specific. In a series of 54 infants with obstructive uropathy, 90% of infants with PUV had a dilated, thick-walled bladder on prenatal US examination, but a keyhole sign had been noted only in 45% (11). Providing urinary drainage in patients with PUV is the main treatment option (12). Obstructive urethral atresia should also be considered in cases with concurrent umbilical cord cysts. Associated congenital anomalies are more common in these fetuses compared to PUV cases. Antenatal treatment methods may not be useful in such cases because the postnatal prognosis is already very poor (13).

All fetuses should be evaluated carefully in terms of potential associated chromosomal and structural abnormalities. To understand the postnatal prognosis, necessary tests for genetic syndromes should be performed after detailed ultrasonography. Presence of additional concomitant anomalies, chromosomal anomalies, early detection and anhydramnios in early gestational weeks are generally related to poor prognosis. Also, laboratory findings are the other important prognostic markers which show the renal function (10). Termination of pregnancy is an acceptable intervention if any bad prognostic criteria are obtained after careful evaluation. In the present study, we have shown that additional chromosomal anomalies, hydrops fetalis and early onset anhydramnios are the main indications for pregnancy termination.

Muller et al. evaluated 68 MC cases and reported that 35 cases were isolated with a rate of 57.3%. There were 3 fetuses with a chromosomal abnormality (2). Our findings are in concordance with these findings. We have shown that an additional abnormality rate was 33.3% among MC cases.

There are some limitations in our study. Firstly, renal functions could not be fully evaluated in all cases because some families refused a postnatal autopsy and some babies lost during follow-up. The difficulties of reaching the information of the patients and the fact that the obtained information is mostly taken from the families verbally, the reliability of the postpartum data is controversial. Because of the insufficient number of patients, it is not possible to reach guiding conclusions about the evaluation of MC cases.

In conclusion, ultrasound is a very important tool in the diagnosis of fetal megacystis. The presence of associated anomalies may increase the rate of chromosomal abnormalities. Therefore prenatal invasive diagnostic methods should be kept in mind to clarify the etiology. VAS should be considered in cases of isolated obstructive megacystis in order to ensure urinary drainage after evaluation of renal functions. Since the prognosis varies considerably according to the underlying cause, fetal megacystis cases should be evaluated by a multidisciplinary approach in a tertiary center which has pediatric urology, genetic and neonatal intensive care units.

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