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ORIGINAL ARTICLE

Factors associated with the survival of fetuses with a prenatal diagnosis of megabladder

Factores asociados a sobrevida de fetos con diagnóstico prenatal de megavejiga

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What do we know about the subject matter of this study?

Prenatal diagnosis of megacystis is a rare condition associated with high mortality. It comprises a wide spectrum of pathologies and degrees of severity, so different factors associated with higher perinatal mortality have been described.

What does this study contribute to what is already known?

This study aims to analyze and discuss the different factors associated with perinatal mortality in a retrospective cohort of patients with prenatal diagnosis of megacystis in a national perinatal referral center.

Abstract

The presence of fetal megacystis in a renal ultrasound may suggest a mechanical or functional bladder outlet obstruction, an uncommon condition with a poor outcome. **Objective:** To determine prognostic factors in fetuses with prenatal diagnosis of megacystis. **Patients and Method:** Retrospective study carried out between 2003 and 2018 in the Orient Perinatal Reference Center (CERPO), University of Chile. Prenatal and postnatal data were analyzed, as well as etiology, pulmonary hypoplasia, medical and surgical treatment, mortality, renal function, and need for renal replacement therapy. The primary variable analyzed was survival at one year, and the secondary ones were renal function and predictors of survival. Statistical analysis was performed using the Mann-Whitney U tests or Fisher test, and a $p < 0.05$ was considered statistically significant. **Results:** Twenty-five fetuses with prenatal diagnosis of megacystis were included. 52% of them presented oligohydramnios and 84% showed renal anomalies. Vesicocentesis was performed in 15 fetuses and vesicoamniotic shunt was

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performed in 5 cases. There were 6 intrauterine fetal deaths (24%) and, among the 19 live births, 9 died soon after birth (36%) and 1 died in the post-neonatal period due to a non-nephron-urological cause. Nine newborns survived by one year of age (36%), seven of them with associated nephron-urological anomaly, and two were healthy patients. Two patients developed chronic kidney disease. The presence of pulmonary hypoplasia was the only factor associated with increased perinatal mortality ($p<0.05$) secondary to oligohydramnios in all cases. Oligohydramnios was not identified as a prognostic factor in this study. **Conclusions:** The prenatal diagnosis of megacystis comprises a wide spectrum of pathologies including conditions with a high perinatal mortality rate to healthy fetuses with transient enlarged bladder without nephron-urological pathology. The only factor associated with increased perinatal mortality was pulmonary hypoplasia.

Introduction

On obstetric ultrasound, the urinary bladder is visible from the tenth week of gestational age (WGA), once fetal urine production has begun, showing an anechogenic oval pelvic structure[1]. In the first trimester of pregnancy, a megacystis is defined as a fetal bladder with a longitudinal bladder diameter (LBD) greater than 10% of the craniocaudal length or greater than 7 mm[2,3]. In the second and third trimesters, it is defined as a distended bladder with failure to empty in an observation period of at least 45 minutes[2,4].

The finding of megacystis suggests a mechanical or functional obstruction to bladder emptying, which may be partial or complete[4]. The international literature reports a survival of fetuses with megacystis of approximately 46%, but these publications exclude pregnancies in which there was a voluntary termination of pregnancy[5]. In relation to the above, the overall fetal survival is unknown, because these casuistries probably exclude the most severe cases or those with the worst prognosis. However, publications report high mortality and compromised fetal renal and pulmonary function in fetuses with prenatal diagnosis of megacystis[6,7,8]. Likewise, spontaneous prenatal resolution of megacystis in up to 8% of pregnancies has been described[4,9,10], supporting the hypothesis of a temporary paraphysiological dilatation of the fetal bladder[11] in healthy patients. Therefore, different variables have been analyzed in search of prognostic predictors[3].

The objective of this study was to determine factors associated with postnatal survival in patients with megacystis.

Patients and Method

Retrospective cohort study of pregnant women and fetuses with prenatal diagnosis of fetal megacystis, registered into the database of the *Centro de Referencia Perinatal Oriente* (CERPO), Medicine Faculty, University of Chile, between April 1st, 2003, and December 31, 2018.

The pregnant women were referred from primary care or referral centers to the CERPO. Once the diagnosis was confirmed, they were admitted and the legal guardian signed an informed consent form, approved by the ethics committee of the *Centro de Referencia de Salud Cordillera Oriente*, authorizing the use of the information for research purposes.

Demographic data, personal and family history, use of alcohol, drugs, tobacco, medications, history of personal and family congenital malformations, history of morbidities, obstetric history, obstetric formula, and history of pathologies in previous pregnancies and current pregnancy were recorded. The date of the last menstrual period, gestational age at diagnosis at admission to the unit, and previous ultrasound scans performed were recorded. At CERPO, multidisciplinary management was performed, including morphological ultrasound, genetic study, psychological support, and complementary studies such as echocardiography, neurosonography, and fetal magnetic resonance as appropriate.

Diagnostic or therapeutic invasive procedures (amniocentesis, cordocentesis, vesicocentesis, or vesicoamniotic shunting) were performed if appropriate, after counseling and authorization through informed consent. Diagnostic vesicocentesis was performed in fetuses with suspected lower urinary tract obstruction (LUTO) without other life-threatening congenital anomalies, for prenatal assessment of renal function to allow selection of patients who might benefit from a vesicoamniotic shunt. The markers of renal function used in this study were fetal urine levels of sodium, chloride, calcium, total protein, B2-microglobulin, and fetal urine osmolarity.

At delivery, Apgar score at 1 and 5 minutes, weight, sex, and postnatal evolution were recorded. In stillbirths that died before delivery, weight, gestational age, and route of delivery were recorded. Follow-up was carried out by a telephone survey recording the evolution

of the newborn, surgical intervention, and survival at 1 and 5 years of life. In case of death, the date of death was recorded and classified as early neonatal mortality (within the first 7 days of life), late neonatal mortality (between 8 and 28 days of life), and post-neonatal mortality (between 28 days and one year of life).

The search for patients in the CERPO database was performed using the word megacystis, including fetuses with a prenatal diagnosis. Patients with no follow-up available at one year of life were excluded from the study. Postnatal follow-up was performed at the Nephrology and Urology Unit of the *Hospital Luis Calvo Mackenna* (HLCM). The following postnatal variables were analyzed: etiologic diagnosis, presence of pulmonary hypoplasia, medical and surgical treatment, mortality, renal function by glomerular filtration rate (GFR) using the Schwartz equation, and need for renal replacement therapy. The main variable analyzed was survival at one year, and the secondary ones were renal function and predictors of survival at one year of life.

Statistical analysis was performed with STATA software version 12.1 to determine measures of central tendency and frequency, Mann-Whitney U test for continuous variables, and the Fisher test for nominal variables. A survival graph was made with a Kaplan Meier curve. A p-value < 0.05 was defined as statistically significant, with a 95% confidence interval.

Table 1. Characterization of patients according to prenatal ultrasound findings and genetic study

Prenatal characteristics	Fetuses with megacystis (25)
Sex (%)	17 male (68) 5 female (20) 3 indeterminate (12)
Gestational age at diagnosis, median (IR)	16+2 SEG (11+3 SEG)
Greater longitudinal bladder diameter, median (IR)*	53.5 mm (20 mm)
Oligohydramnios at diagnosis (%)	7 (28)
Oligohydramnios during pregnancy (%)	13 (52)
Gestational age of oligohydramnios onset	17+6 SEG (5+3 SEG)
Anhydramnios (%)	6 (24)
Kidney disorders (%)	21 (84)
Aneuploidies (%)	4 (31) 13 pacientes con estudio genético
Associated extrarenal malformations (%)	14 (56)
Keyhole sign (%)	6 (24)
Fetal ascites (%)	7 (28)
Signs of prenatal pulmonary hypoplasia (%)	4 (16)

IR: interquartile range. WGA: week of gestational age. *The longitudinal bladder diameter was obtained during the second or third trimester of pregnancy in all patients.

Results

The total number of patients admitted to CERPO between April 1st, 2003, and December 31, 2018, was 2,328, of which 27 had prenatal diagnosis of megacystis (1.2%), and 2 patients were excluded due to the absence of postnatal follow-up at 1 year.

Twenty-five fetuses with prenatal diagnosis of megacystis with prenatal ultrasound findings and genetic study were included (Table 1). The median gestational age (GA) at diagnosis was 16 + 2 weeks and in 68% (17/25) the diagnosis was made before referral to CERPO. Fifty six percent of patients (14/25) were diagnosed before 18 gestational weeks (early megacystis) and the remaining 44% (11/25) after 18 gestational weeks (late megacystis). Six fetuses were diagnosed during the first trimester of pregnancy and, out of these, 5 patients had an LBD greater than 12 mm (range 12 to 29 mm, mean 23 mm).

Of the cases, 52% (13/25) had oligohydramnios (OHA) during pregnancy and 85% (11/13) of them before 26 weeks. Only 2 patients with OHA before 26 weeks survived at 1 year.

During gestation, 84% of patients (21/25) presented the following ultrasound renal anomalies: hydronephrosis or hydroureteronephrosis (16/25), renal dysplasia (6/25), horseshoe kidney (1/25), renal atrophy (1/25), and multicystic kidney (1/25).

Vesicocentesis and fetal urine analysis were performed in 56% of the patients (14/25) and amnioinfusion in 2/25 cases. A genetic study for suspected aneuploidy was performed in 52% of the cases (13/25), of which 4 patients presented positive results (1 case of trisomy 13 and 3 cases of trisomy 18).

A vesicoamniotic shunt (VAS) was placed in 5 patients with OHA. In 4 of them, the megacystis reversed and all had initial improvement of amniotic fluid. Subsequently, 2/5 fetuses developed OHA and anhydramnios. In this group, the perinatal outcome was 1/5 stillborn, 2/5 neonatal death, and 2/5 alive at 1 year with Prune Belly syndrome. Complications associated with VAS in these patients were 1 case of obstruction and 1 of VAS displacement.

In 20% (5/25) of the patients, there was spontaneous resolution of the megacystis, however, 2 cases persisted with OHA. Spontaneous resolution of megacystis was before 23 weeks in 3 patients, of which 2 survived at 1 year. On the other hand, in 2 patients the megacystis resolved after 23 weeks, but both were neonatal deaths.

The overall perinatal outcome was 24% (6/25) stillborn, 36% (9/25) early neonatal death, 4% (1/25)

post-neonatal death, and 36% (9/25) survive at 1 year. Of the 19 live births, early neonatal deaths (9/19) had a significantly lower gestational age at birth compared with patients who survived the neonatal period (10/19) (mean 33 WGA (30-37 WGA) vs 37 WGA (34-40 WGA) respectively, p 0.0049). Seven live-born patients had pulmonary hypoplasia at birth and of these 6 were early neonatal deaths.

In the post-neonatal period, one patient died at 8 months secondary to other pathologies with a polymalformative syndrome associated with an isolated urological alteration (13 mm left hydronephrosis) and normal renal function, and 9 patients survived at one year of life (36%).

When comparing different prenatal variables, fetal urinalysis, and the presence of pulmonary hypoplasia in the group of stillborns and neonatal death patients versus patients alive at one year (Table 2), only the presence of pulmonary hypoplasia at birth was related to higher neonatal mortality (p 0.025). Fetal urinalysis was performed only in 14 patients where renal function markers were measured. Sodium < 100 mmol/L, chlorine < 90 mmol/L, calcium < 8 mg/dL, total protein < 20 mg/dL, B2-microglobulin < 4 mg/L and osmolarity < 200 mg/L were considered normal reference values, suggesting preserved fetal renal function. However, these parameters were out of the normal range in most patients at the time of vesicocentesis, showing no significant differences between the group of stillborns-neonatal deaths patients and patients alive at 1 year.

The patients were classified into 3 groups according to the etiology of their megacystis as LUTO, complex megacystis (those associated with syndromes, aneuploidies, or multiple malformations), and isolated urological alteration or healthy urinary tract (Table 3). Patients with complex megacystis presented the worst survival rate at one year (9%), compared with patients with isolated LUTO (56%) and isolated urological alteration or healthy urinary tract (100%) (Figure 1).

The postnatal follow-up of the 9 patients alive at 1 year was an average of 6 years (range 1 to 16 years). Renal function at 1 year of life was normal in 2/2 patients who had no nephro-urological pathology and in 3/7 patients who did have it. The remaining 4 patients with postnatal nephro-urological pathology had an average GFR of 43 ml/min (range 15-72 ml/min) at 1 year of life.

The patients with nephro-urological pathology had a mean nadir serum creatinine level (the lowest recorded in the first year of life) of 0.65 mg/dL (range 0.27 to 1.72), and the 2 patients who had end-stage renal disease presented the highest values during follow-up (0.77 and 1.72 mg/dL). The latter, with postnatal diagnosis of Prune Belly syndrome and posterior urethral valves (PUV), required renal replacement therapy at 28 and 6 months of age, respectively, and were subsequently transplanted. The remaining 5 patients with nephro-urological pathology had a mean GFR of 103 ml/minute (79-132) at the end of the mean follow-up of 6 years (range 14 months to 10 years).

Table 2. Comparison of prenatal variables and presence of pulmonary hypoplasia at birth between the group of stillborns-neonatal deaths patients and patients alive at 1 year of age.

Variable	Stillborns-neonatal deaths (15)	Alive at 1 year of age (9)	p
Female sex	2 (17%)	2 (22%)	0.586
GA at diagnosis	16+6 SEG (12-27)	24+4 SEG (9-38)	0.1523
OHA	10 (67%)	3 (33%)	0.122
GA of OHA onset	18+5 SEG (12-30)	24+1 SEG (17-35)	0.3105
Anhydramnios	5 (33%)	1 (11%)	0.238
Kidney anomalies	13 (87%)	7 (78%)	0.486
Aneuploidy	4 (50%) 8 pacientes estudiados	0 (0%) 5 pacientes estudiados	0.098
Longitudinal bladder diameter	57 mm (12-118 mm)	62 mm (42-120 mm)	0.7466
Associated malformations	9 (60%)	4 (44%)	0.375
Keyhole sign	4 (27%)	2 (22%)	0.603
Fetal ascites	5 (33%)	2 (22%)	0.461
Antenatal pulmonary hypoplasia	4 (27%)	0 (0%)	0.128
Vesicocentesis	9 (60%)	5 (56%)	0.582
VAS	3 (20%)	2 (22%)	0.640
Pulmonary hipoplasia in live birth newborns	6 (67%)	1 (11%)	**0.025**

GA: gestational age. OHA: oligohydramnios.VAS: vesicoamniotic shunt.

Table 3. Mortality of patients with prenatal megacystis according to etiological group

Etiological group according to mortality	Stillbirth (6)	Early neonatal mortality (9)	Late neonatal and post-neonatal mortality (1)	Alive at 1 year of age (9)
LUTO (9) PUV and urethral atresia	1 LUTO	2 Prune Belly syndrome 1 LUTO	0	3 Prune Belly syndrome 2 LUTO
Complex megacystis (11) Associated with syndromes, aneuploidies or multiple malformations	2 Trisomy 18 1 Trisomy 13	4 Polymalformative syndrome* 1 Trisomy 18 1 Sacrococcygeal teratoma with fetal hydrops	1 Polymalformative syndrome	1 Polymalformative syndrome **
Healthy urinary tract or isolated urological anomaly (3)	0	0	0	2 Healthy 1 Left refluxing obstructive megaureter
Indeterminate (2)	2 Indeterminate	0	0	0

PUV: posterior urethral valves. LUTO: low urinary tract obstruction. *Associated with Potter syndrome in 2 cases and with caudal regression syndrome in 1 case. **Associated with Prune Belly syndrome and anorectal malformation.

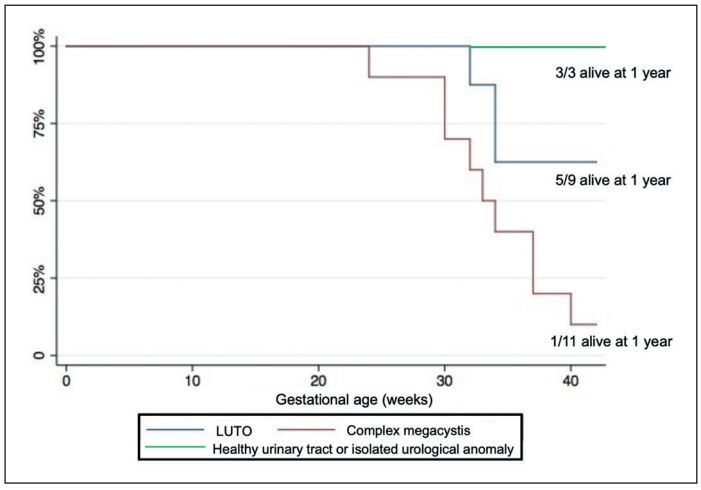

Figure 1. Survival of patients with prenatal diagnosis of megacystis according to etiology. LUTO: low urinary tract obstruction.

Discussion

The prevalence of megacystis on prenatal ultrasound has been reported in 0.06 to 0.4% of pregnancies[3,12] and in 0.38% of live new borns (46 in 12,000 births)[2]. The etiology is related to gestational age and the main cause of megacystis at any gestational age is LUTO. However, it may be related to many other conditions, including complex conditions of poor prognosis such as Prune Belly syndrome, Berdon syndrome, megalourethra, and cloacal malformations with urethral stenosis, but also isolated alterations of good prognosis[4,13,14,15].

Recently, a Dutch multicenter study found that one-third of patients with megacystis presented complex anomalies or associated chromosomal alterations, with anorectal malformation (8% of cases) as the most frequent complex anomaly[15]. This is consistent with the results of this study, where 44% of patients had complex megacystis associated with aneuploidy and multiple malformations including anorectal malformation and caudal regression syndrome, with survival at one year in only one of these patients (9%). Patients with isolated LUTO (not associated with malformation syndromes or aneuploidies) presented a better survival at one year (56%) but in our study, as a perinatal referral center, this only accounts for 36% of the cases.

The presence of aneuploidy has been estimated in approximately 15% of patients with megacystis, including trisomy 18, 13, and 21[9,12], which is associated with a poor perinatal prognosis. Between the 11 and 14 weeks, it is recommended to perform a genetic study in fetuses with megacystis, especially with a 7 to 15 mm of LBD, since most chromosomal alterations occur in this group[10,16]. In this series, prenatal karyotype study was performed only in 52% of patients, all after 14 WGA, where 4 presented aneuploidies (1 trisomy 13 and 3 trisomy 18), which may be underestimated by the high number of stillborns and neonatal deaths in the group without genetic study (58%) and with associated malformations (56%). Therefore, we recommend a genetic study in patients with megacystis in the first trimester of pregnancy and for those with other associated malformations or suspected aneuploidy (complex megacystis).

Megacystis magnitude has been associated with increased mortality, especially an LBD greater than 15 mm in the first trimester of pregnancy[3]. In this study, in only 6 patients the LBD was measured in the

first trimester of pregnancy, probably due to the late referral, and all but one case had an LBD greater than 15 mm. Gestational age influences the LBD. Table 1 shows the highest average value measured in all cases during the second or third trimester of gestation. In this study, the LBD measured in the second and third trimesters was not associated with higher perinatal mortality as has been described in measurements in the first trimester.

In the prenatal period, in fetuses with LBD of 8-12 mm in the first trimester, up to 80% of spontaneous resolution of megacystis has been reported[4,9,10]. A recent meta-analysis showed a spontaneous resolution of 40% of megacystis in fetuses diagnosed before 18 weeks[12]. These data support the hypothesis of a temporary paraphysiological dilatation of the fetal bladder[11], probably secondary to the absence of autonomic innervation of the bladder since smooth muscle fibers appear only after 13 weeks of gestation[17]. In our series, patients diagnosed with megacystis in the first trimester had an LBD greater than 12 mm, with no spontaneous resolution.

In 5 patients with a diagnosis of megacystis from the second trimester onwards, spontaneous resolution was observed; however, in all of them, the presence of LUTO or complex megacystis was confirmed. Recently, Fontanella et al published a series in which all cases with spontaneous resolution before 23 weeks of gestation were of good prognosis without major urologic sequelae[17]. In our series, 3 patients had spontaneous resolution before 23 weeks, however, all developed major urologic sequelae.

In fetuses with megacystis, the presence of OHA implies a poor prognosis due to the associated pulmonary hypoplasia[9], because pulmonary development depends on an adequate volume of amniotic fluid[11,18]. A recent meta-analysis and a multicenter study determined that the lower the gestational age at the onset of OHA, the worse the fetal outcomes related to fetal and neonatal survival[12,15]. In our series, more than half of the patients presented OHA during pregnancy; however, there were no statistically significant differences in relation to the gestational age at the onset of OHA nor the presence of OHA or anhydramnios regarding survival. However, the presence of the association OHA-pulmonary hypoplasia at birth was related to higher neonatal mortality (p 0.025).

These results may seem contradictory; however, it should be considered that of the 12 patients without prenatal OHA, 4 presented aneuploidy (Trisomy 13 and 18) of poor perinatal prognosis resulting in 3 stillborns and one newborn who died in immediate postpartum care. In contrast, none of the 13 patients with prenatal OHA presented aneuploidy or life-threatening malformations.

Other factors associated with poor prognosis of renal function are kidneys with reduced parenchymal thickness and the presence of renal cysts. Early renal histopathologic changes are associated with greater involvement of subsequent renal development[2,13]. In our series, most patients presented prenatal renal anomalies, with upper urinary tract dilatation (64%) and renal dysplasia (24%) as the most frequent. The keyhole sign, a component of the classic LUTO triad in prenatal diagnosis, was observed in only 6 patients, of which only one presented PUV, in agreement with a previous study that has described this sign as a poor predictor of PUV[19].

In patients with LUTO, the analysis of fetal urine through vesicocentesis allows a better prenatal assessment of renal function and a better selection of fetuses that could benefit from fetal interventions[20,21]. In this series, only 56% of patients had prenatal renal function studied and it was not possible to determine whether these markers were associated with a worse prognosis regarding survival. A recent systematic review based on studies with few patients and variable cut-offs for the different markers concluded that the analysis of none of the markers in fetal urine had a clinically significant value in predicting postnatal renal function[22]. However, some authors suggest implementing these fetal urine markers with cut-off levels according to gestational age to improve parental counseling, considering that in many countries parents can choose voluntary termination of pregnancy[23].

Intrauterine therapy would not be indicated in a fetus with another life-threatening congenital anomaly. For this reason, adequate ultrasound evaluation of the fetus with megacystis and genetic study in suspected aneuploidy is essential. Amnioinfusion is recommended in cases where ultrasound evaluation is limited due to OHA[24]. In this study, it was performed in two patients; one with anhydramnios and bilateral multicystic kidneys who died during the first hours of life due to pulmonary hypoplasia and the other one with OHA and postnatal Prune Belly syndrome with survival at one year of life.

Several prenatal therapies have been described to improve neonatal survival and prevent renal failure in fetuses with megacystis. Among them, VAS is a treatment alternative that has been shown to improve fetal survival in these patients, but not future renal prognosis[25]. There is consensus that the most suitable candidates for VAS are patients with normal karyotype, absence of other congenital anomalies, presence of OHA, and favorable urinalysis[10]. In our series, the placement of VAS was associated with improvement of OHA and resolution of megacystis in most of the cases. However, it was not free of complications including

recurrence of OHA and obstruction and displacement of the VAS.

In this series, survival at one year of life was 36%, mainly related to a high rate of prenatal and early neonatal mortality associated with pulmonary hypoplasia. However, prematurity should be considered as an important associated factor in mortality; early neonatal death had a significantly lower gestational age at birth than those who survived the neonatal period.

The most frequent etiology of the patients with survival at one year was LUTO, mostly Prune Belly syndrome. Except for two patients who required renal replacement therapy in the first years of life, the rest of the patients with survival at one year had good renal function at the end of the follow-up.

Survival of patients with megacystis in this study seems to be strongly determined by the etiologic group of their megacystis. Patients with complex megacystis had the worst survival at one year (9%) with higher stillbirths and early neonatal mortality compared with patients with isolated LUTO (56%). All cases with isolated urological alteration or with healthy urinary tract in the postnatal period survived at one year and had good renal function at the end of the follow-up.

The limitations of this study include the small number of patients in the series, secondary to the low frequency of this condition in a perinatal referral center, and its retrospective nature. However, it is the first national series reported on this condition, which will contribute to improving local knowledge of this rare nephro-urological pathology and will allow us to make a more accurate diagnosis, provide more complete counseling, and offer the best therapeutic alternatives to our patients.

Conclusions

Prenatal diagnosis of megacystis comprises a wide spectrum of pathologies, from conditions with high mortality to healthy patients with transient bladder dilatation. Mortality at one year of life in our series reached 64% and the presence of pulmonary hypoplasia at birth was associated with higher perinatal mortality.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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