

## REVIEW ARTICLE

# Prune-belly Syndrome versus Posterior Urethral Valve

<sup>1</sup>Fernando Bonilla-Musoles, <sup>1</sup>Francisco Raga, <sup>1</sup>Francisco Bonilla Jr, <sup>2</sup>Luiz Eduardo Machado  
<sup>3</sup>Newton G Osborne, <sup>1</sup>Fernando Ruiz, <sup>1</sup>Juan Carlos Castillo

<sup>1</sup>Department of Obstetrics and Gynecology, University of Valencia, Valencia, Spain

<sup>2</sup>School of Medicine, University of Salvador (BA), Brasil, Brazil

<sup>3</sup>School of Medicine, University of Panama, Panama City, Panama

**Correspondence:** Fernando Bonilla-Musoles, Department of Obstetrics and Gynecology, Medical School, University of Valencia Blasco Ibañez 17, 46010 Valencia, Spain, e-mail: profesorbonillamusoles@hotmail.com

## ABSTRACT

Recent development of three-dimensional (3D) and four-dimensional ultrasound (4D), specially using tomographic ultrasound image (TUI), inverse mode, automatic volume calculation (AVC) and virtual organ computer-aided analysis (VOCAL), provided us with new possibilities to study fetal low urinary obstructions before 24th week. Ultrasound scan studies have been conducted in order to provide information about prune-belly syndrome and posterior urethral valves (PUV). The purpose of this paper is to give brief anatomical, histological and ultrasound review to use 3D and 4D US in the assessment of both syndromes.

### Objectives:

- Define possibilities to differentiate with ultrasound between fetal prune-belly (PB) and posterior urethral valves (PUV) syndromes.
- Describe the ultrasound images and accompanying malformations in both syndromes.
- Evaluate the value of different US modes for differential diagnoses.

**Keywords:** Prune-belly, Posterior urethral valves, Three-dimensional/Four-dimensional sonography.

## INTRODUCTION

Prune-belly syndrome (PBS) is a rare, congenital, obstructive, urologic alteration that is associated with megacystic bladder and visible deformity of the abdominal wall. It is frequently associated with other fetal malformations.<sup>1</sup> It is one of the fetal obstructive uropathies, which consist of a heterogeneous group of malformations that are characterized by major or minor dilatation of the urinary tract along with renal insufficiency.

Fetal obstructive uropathies are classified as prerenal (associated with intrauterine growth restriction, fetofetal transfusion syndrome, nonsteroidal antiinflammatory agents, cocaine, etc.), renal (renal agenesis, multicystic renal dysplasia, and polycystic kidneys), and postrenal (obstructive uropathy and vesicoureteral reflux).

Fetal obstructive uropathies may be bilateral or unilateral, intrinsic or extrinsic, high (pyeloureteral), middle (uretero-vesical) or low (urethral). A "functional" type of obstruction has been proposed where the urethra offers more resistance than bladder contractions are able to overcome.<sup>1</sup>

PBS belongs to the group of obstructive uropathies that may be unilateral or bilateral. They are extrinsic in nature and usually associated with low obstruction. They commonly result from an early distal urinary stricture or obstruction, but may be associated with other conditions. The name refers to the peculiar abdominal wall appearance that almost always (but not always) has a distended and crumpled skin that looks like a prune.<sup>2</sup> About 97% of cases occur in male fetuses<sup>2,3</sup> and it is reported



**Fig. 1:** 2D/3D/4D and macroscopic view of a case of PBS (personal case)

to occur four times more frequently in twin than in singleton gestations<sup>1,4</sup> (Fig. 1).

The incidence of PBS is estimated to be 1 in 30,000 to 50,000 newborn babies.<sup>1,4</sup> However, the incidence is likely to be greater since many fetuses die *in utero* or are aborted,<sup>2,3,6-8,37</sup> especially when the syndrome is diagnosed early in the gestation.<sup>8</sup> Although some cases have been described in families, the cases are essentially sporadic. There are a few more than 800 described in the English literature.<sup>2,3,5-15</sup>

PBS is characterized by the following triad:

- Anterior abdominal wall distention with deficiency (70%) or absence (30%) of its musculature,<sup>2,36</sup> which is substituted by connective tissue. The anterior abdominal wall is therefore extremely thin,<sup>3,8</sup> and as the bladder megacyst protrudes, the abdomen becomes much more prominent than the thorax.
- Genitourinary anomalies: There is always a megacystic bladder, a dilated prostatic urethra with hypoplasia or atrophy of the prostate, and a small verumontanum. There is urethral obstruction with dilatation of the prostatic segment of the urethra.<sup>12</sup> There is in addition renal hypoplasia or dysplasia, ecstasic megaureters with thickened walls, and frequently, there are focal areas of ureteral stenosis and gigantism. The vesicoureteral union is usually open with reflux in 75% of cases. Between 25 and 50% have an open urachus or urachal diverticulosis.<sup>2</sup> Bilateral cryptorchidism occurs in 95% of cases.<sup>13,37</sup> In female fetuses, there is urethral atresia, which favors an obstructive etiology.
- Pulmonary hypoplasia: More than 97 of cases are male<sup>2,3</sup> and only males develop the complete syndrome. The incidence is four times higher in twin gestations than in singleton pregnancies.<sup>4,20</sup> The syndrome is extremely rare in females with only 10 published cases in the medical literature,<sup>11</sup> and there is a question as to whether these cases represent ventrolateral herniations.

PBS receives its name due to the peculiar appearance of the anterior abdominal wall, which presents almost always (but not always) with a distended, usually wrinkled skin that is similar to a “prune”.<sup>2</sup>

## HISTORY

The first description of prune-belly syndrome was in Würzburg, Germany in 1839.<sup>16</sup> The authors described newborn babies with absence of abdominal wall musculature, especially involving the lateral muscles (Der Mangel der Muskeln, insbesondere der Seitenbauchmuskeln). It was subsequently described by Parker in an infant in whom some of the abdominal wall muscles were absent.<sup>17</sup>

Subsequently, more complete reports in the pediatric literature gave this abdominal wall malformation names like Fröhlich’s syndrome,<sup>16</sup> abdominal wall deficiency syndrome, congenital absence of abdominal wall muscles, Eagle-Barrett syndrome –who re-examined nine other cases and defined the triad,<sup>18</sup> Obrinsky syndrome,<sup>19</sup> urethral obstruction malformation complex,<sup>37</sup> and syndrome of the triad.<sup>20</sup>

## PATHOGENESIS

The pathogenesis of prune-belly syndrome is not clear. Several hypotheses have been proposed:

1. The best known and most challenged is the hypothesis that PBS is of a mechanical origin. It is the consequence of stenosis or obstruction of the distal urinary tract at the level

of the urethra, which is initiated between the sixth and eighth week of embryonic life.<sup>2,12-14</sup> As a consequence, distention of the urinary bladder, the ureters, and the kidneys would appear. The initial urethral obstruction would lead to degeneration of the abdominal wall musculature. According to this hypothesis, the urinary bladder distention that results from urethral obstruction secondarily prevents development of the abdominal wall muscles and causes their degeneration.<sup>12</sup> The lack of testicular descent would also result from urinary bladder distention.<sup>13</sup>

2. New evidences suggest a primary somatic defect with incomplete differentiation or failure of migration of the lateral somite mesoderm before the establishment of lateralization, possibly in the abdominal muscles that originate from the first lumbar myotome.

PBS would then be caused by a delay or maldevelopment of the mesoderm between the sixth and the eighth week of gestation due to any type of damage (i.e. teratogenic insult, genetic mutation, chromosomal alteration, infection, etc.). As a consequence, there is an abnormal development of the urogenital system and of abdominal musculature.<sup>1</sup> This defect in mesenchymal development early in gestation would account for an abnormal development of the prostate, of the urinary tract musculature, of gubernaculum, and of the abdominal wall musculature.

Microscopic studies have shown profound alterations in abdominal and urinary tract musculature, as well as degeneration and fibrosis.<sup>37,38</sup> PBS sequence is then considered to be secondary to connective tissue and smooth muscle abnormalities that are the root causes of bladder distention and oligohydramnios.<sup>21</sup> An interesting histological study that compared normal cases with phenotypic prune-belly and with posterior urethral valve cases revealed important differences between the normal cases and the PBS and posterior urethral valve (PUV) cases, which support this theory.<sup>37</sup>

In PBS cases, the bladder’s muscular tissue would be diminished while connective tissue is increased. These are therefore fibrotic and scantily muscular bladders (5 out of 8 cases). Curiously, three cases with scant connective tissue and with an increase in muscular tissue presented with inferior urinary tract obstruction, a finding very similar to what is seen in cases of PUV. In PUV cases, the bladder muscular tissue is markedly increased while the connective tissue is mildly increased (4 cases). In adults, the bladder’s response to obstruction is trabeculation due to hypertrophy of muscular tissue with infiltration of connective tissue between the muscular layers.

A primary somatic defect explains the numerous malformations of other organs that frequently occur with prune-belly syndrome.<sup>2,14</sup> According to this theory, there would be a primary interference with normal development of the abdominal wall musculature. Bladder distention and hydronephrosis are then the result of defective musculature and associated poor peristalsis of these muscles. However,

the appearance of PBS with abdominal distention due to ascites or other causes suggests that phenotype is merely the end result of stretching the abdominal wall during development and bears no relationship to abnormal mesenchyme.<sup>37,38</sup>

3. The proposed inheritance patterns include sporadic occurrence, familial, sex-limited expression of an autosomal dominant X-linked recessive gene.<sup>10,12</sup>
4. Abnormalities of the allantois due to an unusual lengthening or to an ample implantation base of the abdominal wall. This concept is based on the increased frequency in omphalocele cases.<sup>22</sup>
5. Abnormal, persistent fixation of the bladder to the umbilicus. A persistently patent urachus.<sup>9,38</sup>
6. A case of aganglionosis.

### PROSTATE DEVELOPMENT IN PBS AND PUV

The initial abnormal development of the prostate is the cause of ultrasonographic differences that are found between these two pathologies. The male urethra is divided into five anatomic divisions. The glandular portion, the cavernous or penile portion, and the bulbous portion form the anterior urethra. The prostatic portion (the part within the prostate gland) and the membranous portion (the short part traversing the pelvic floor) are the posterior urethra. It is with the posterior urethra that we are mainly concerned in this work.

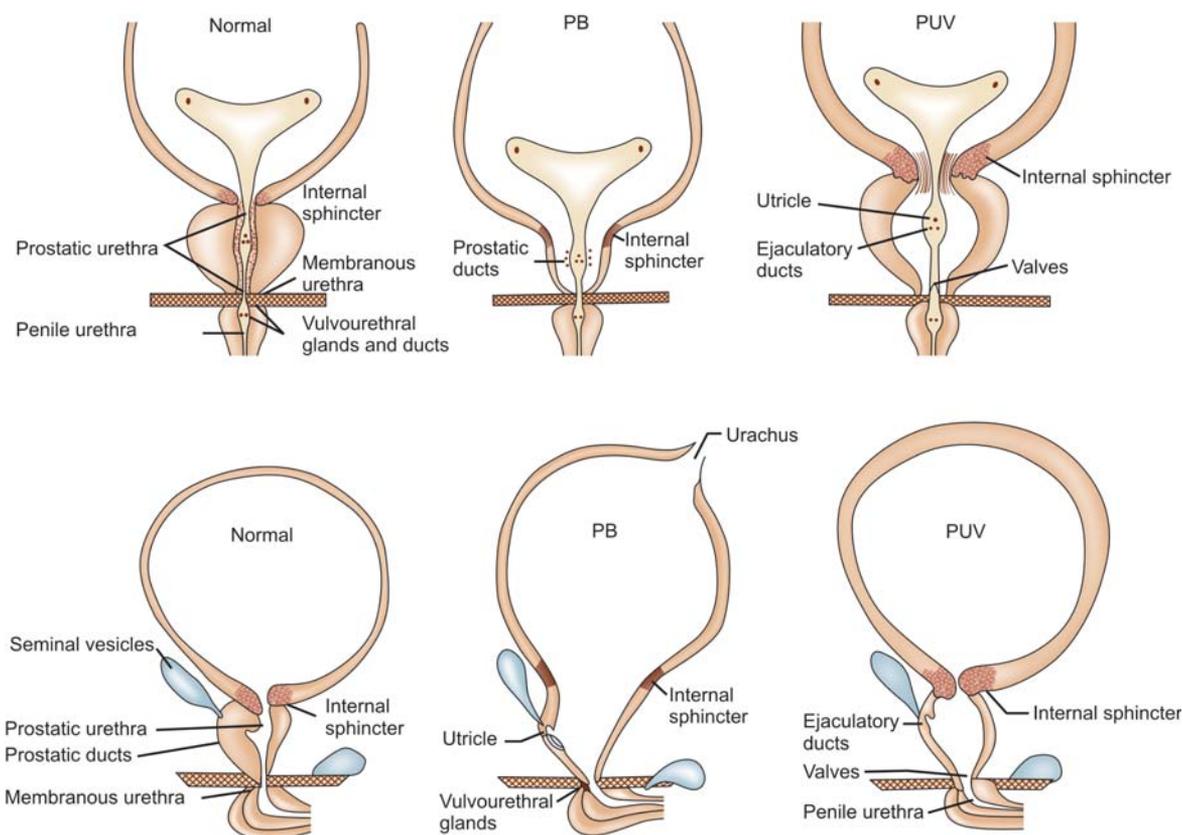
An extraordinary comparative anatomic study between normal fetuses and fetuses with PBS and with PUV has allowed

a better understanding of these complex syndromes.<sup>1</sup> In cases of PBS, the prostatic urethra is extremely dilated and there is no clear definition between the base of the bladder and the prostate resulting in a funnel-shaped urethra. No prostate tissue is recognized although the verumontanum and the seminal vesicles are present. Obstructive lesions of the lower urinary tract are identified in all cases of PUV (urethral stenosis or atresia, multiple urethral lumens, urethral diaphragms, and combinations). Light microscopy reveals aberrant prostatic development and the amount of smooth muscle appears decreased.

In cases of PUV, the prostatic urethra is moderately to markedly dilated. The junction between the bladder and prostatic urethra is well demarcated with a conspicuous ridge of muscle. Light microscopy also reveals an aberrant prostatic development, but different from what is seen in PBS.

Acinar development is limited to the periphery of the prostate in the posterior and lateral regions and the anterior fibromuscular stroma is present as a band of smooth muscle surrounding the utricle and ejaculatory ducts. The stroma of the periurethral zone is also normal. The internal bladder sphincter is composed of hypertrophic bundles of smooth muscle.

Grossly, the prostates of individuals with PBS and with PUV are distinctly different primarily at the junction of the base of prostate with the bladder. In PBS, the bladder neck is noted to be markedly dilated resulting in a wine glass or a funnel configuration. In contrast, bladder neck hypertrophy is a



**Fig. 2:** Anterior and lateral diagrammatic representation of the prostate, prostatic urethra, and internal bladder sphincter in PBS and PUV as compared to normal. The presence or absence of the internal sphincter is helpful in distinguishing the two syndromes (Adapted from reference 1)

common response to urethral obstruction in these cases (Fig. 2). The gross and ultrasonographic features result from either abnormally small (in cases of PBS) or abnormally large (in cases of PUV) smooth muscle bundles.<sup>1</sup>

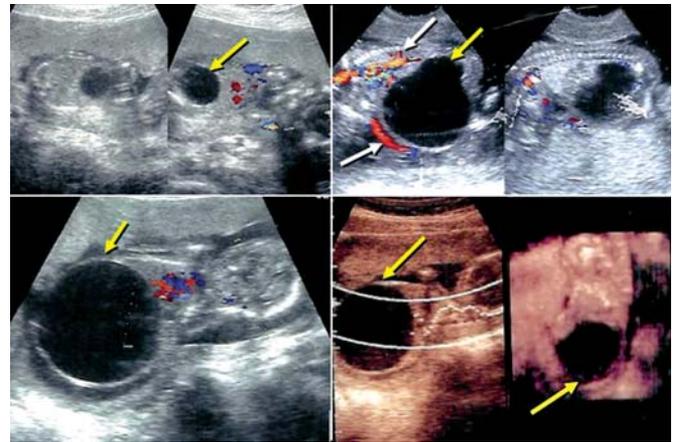
### OBSERVATIONS WITH VAGINAL AND ABDOMINAL 2D ULTRASONOGRAPHY

- Abdominal distention with a thin abdominal wall.
- A large bladder, also with a thin wall, and dilatation of the entire urethral length (in contrast to the dilatation of urethral valves of the posterior segment of the urethra in PUV) (Fig. 3).
- One must look for the keyhole sign for a differential diagnosis and an attempt must be made to distinguish between the rounded and keyhole forms (Fig. 4).
- We must point out that it is difficult to visualize the area of stenosis with ultrasound in PBS cases due to the dilatation of the bladder and abdominal wall.<sup>6</sup>
- Hydronephrosis (unilateral or bilateral).<sup>3</sup>
- Oligohydramnios (not always) (Figs 1, 3 and 4). It may be absent in the first trimester.
- Bilateral cryptorchidism (difficult to see when there is oligohydramnios or in early gestations).
- Pulmonary hypoplasia. Very easy to see (Figs 1, 3, and 4).

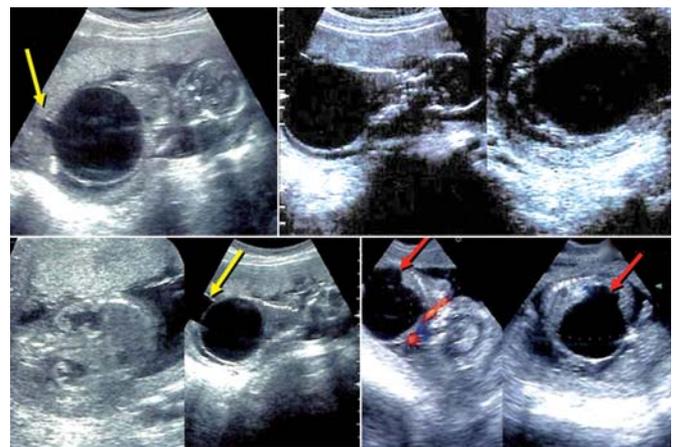
Urine production starts between gestational weeks 8 and 10. For this reason the earliest gestational age when urine production can be seen is in week 11.<sup>22-24</sup> Detection prior to week 14 is infrequent since at these gestational ages it is difficult to observe other malformations besides abdominal distention and enlarged bladder. For example, Chen<sup>3</sup> described 6 cases between 13 and 22 weeks over a five year period. There was bladder distention in all six cases but other abdominal organs could not be seen.

Although testicular descent starts on week 12, they do not arrive in the scrotum before week 13. For this reason it is impossible to diagnose cryptorchidism prior to week 13.

- If there is suspicion, it is convenient to use Doppler and 3D/4D with VOCAL, inverse, and tomographic ultrasound imaging (TUI).  
One must look for an enlarged bladder with or without a keyhole sign, hypoplasia-aplasia of the abdominal wall, and cryptorchidism.
- PBS encompasses a wide and diverse spectrum of fetal anomalies. For this reason:
  - i. There must be a careful study of the characteristics of the abdominal tumor.
  - ii. There should be an attempt to determine the level of obstruction taking into account that vesicoureteral reflux is common in 88% of these cases.
  - iii. The kidneys must be studied and their sizes and echo-structures investigated. The presence of cysts in the cortex is a marker of severe renal dysplasia.
  - iv. Serial evaluation of amniotic fluid must be made as this will be an indicator of fetal diuresis. Oligohydramnios is a sign of poor prognosis. The presence of normal amniotic fluid rules out lethal forms, but does not



**Fig. 3:** Four cases of PBS. A keyhole is not seen in any of these. All have a megacyst with a very thin and homogeneous bladder wall. All have pulmonary hypoplasia. Only one (upper right) has an elongated shape or nut shape which would correspond to Johnson's type C. Doppler scanning shows the vessels displaced by the tumor



**Fig. 4:** Four other early cases of megacystis. The yellow arrows show the keyhole sign in two of these cases and two others show megabladder in an oval form (red arrows). It is impossible to detect different thicknesses of the bladder wall, as was referenced. All walls are very thin as is also the case with the abdominal wall

guarantee normal renal function. Acute oligohydramnios in the third trimester may indicate acute renal failure.

- v. The fetal sex must be determined. Detection of female genitalia suggests an ovarian cyst or a cloacal malformation. Male genitalia suggest PUV or PBS.
- vi. Other fetal abnormalities must be ruled out since their incidence increases in cases of low obstructive uropathy.

Morphologic ultrasonography can be very difficult, if not impossible, when there is severe oligohydramnios. In these cases, amnioinfusion (Ringer's lactate solution at 37 degrees centigrade) will facilitate the evaluation of fetal structures. The results are not as good if saline or a solution of dextrose are used.<sup>25</sup>

- Evaluation of the bladder with Doppler, 3D with orthogonal planes, and 4D with VOCAL mode helps with the diagnosis and suggests the cause of the enlarged bladder<sup>3,26-29</sup> and in adults,<sup>30</sup> abdominal distention is more evident and thoracic compression can be observed. The marked attenuation of the abdominal and bladder walls can be appreciated and

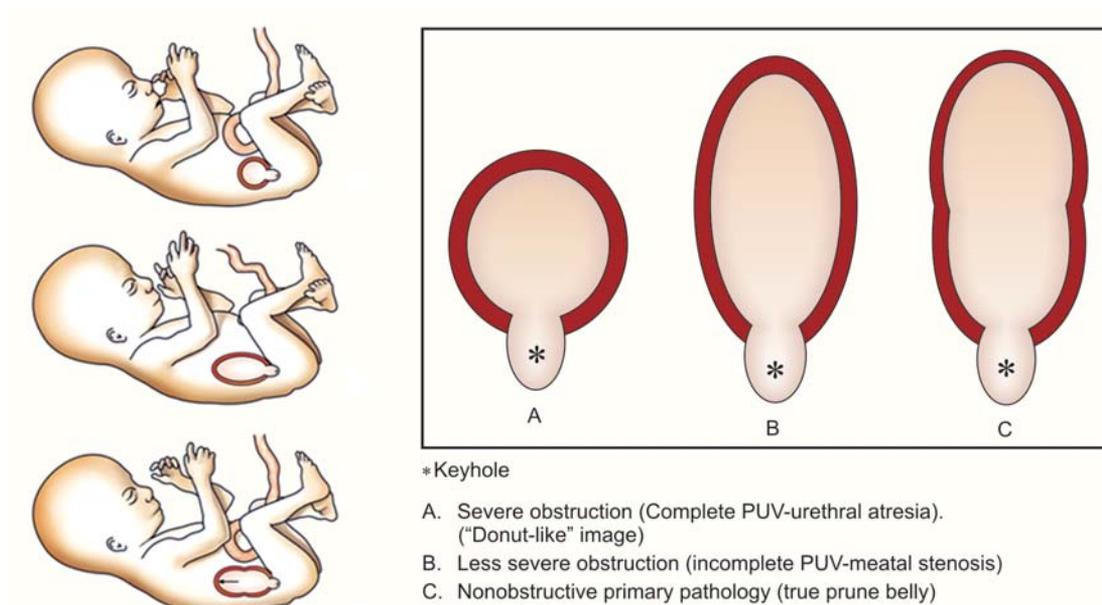


Fig. 5: Image of the bladder with US after amnion drainage<sup>31</sup>

the keyhole sign can be seen.<sup>6</sup> Doppler scanning allows visualization of peritumoral vascular distribution and the severity of renal lesion.<sup>3,8</sup>

Three ultrasound signs can be seen (Fig. 5):

- The "donut-like" image (thick, rounded walls), where the bladder walls are thickened in the inferior portion (corresponding to the bladder neck) and thinned out in the superior part (corresponding to the main portion of the bladder). Between both parts, a communicating groove can be appreciated. This pattern is present with severe obstructions as seen with urethral atresia or with PUV.
- A tubular bladder with thick walls that are symmetrically lengthened. This form is associated with less severe obstructions due to anomalies of the urethral meatus or to incomplete PUV.
- The "keyhole" bladder image, which is seen with PUV.

### OTHER COEXISTING MALFORMATIONS

More than 75% of PBS or PUV cases are associated with other fetal anomalies.<sup>3,33,38</sup> In its more severe form, the syndrome affects exclusively males. The defect is variable and may be asymmetrical oscillating between mere hypoplasia to complete absence of abdominal wall musculature. Generally, the oblique muscles and the suprapubic portion of the recti are intact. The umbilicus may have an upward protrusion.

#### Genitourinary Tract Alterations

When the syndrome is complete, there are multiple alterations of the genitourinary tract<sup>38</sup> (Fig. 6). The kidneys tend to be dysplastic, cystic, hypoplastic, or with hydronephrosis. They are frequently asymmetric. When renal function is preserved, they tend to deteriorate slowly.

The ureters, which in the majority of cases have vesico-ureteral reflux, are usually dilated and stretched and have poor contractility. In some cases they are atretic.



Fig. 6: Polycystic kidneys, diaphragmatic hernia, and presence of intestinal loops in the thoracic cavity

The urinary bladder is dilated and extends to the umbilicus. The urachus remains patent. Frequently, urine refluxes to the urachus. There is rarely an obstruction or atresia of the bladder neck.

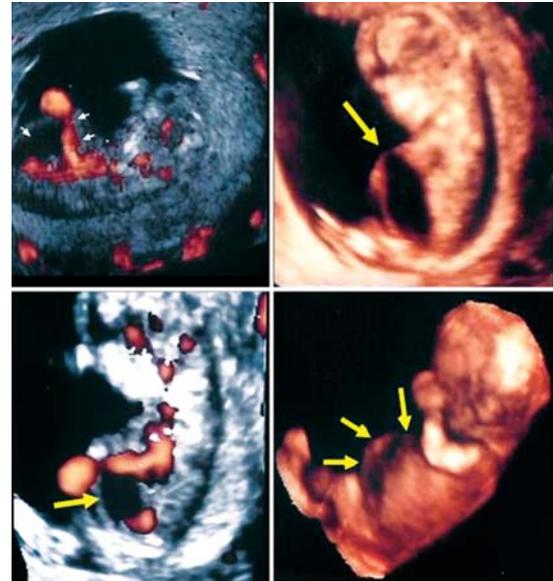
In cases where the origin of the problem is caused by an obstruction of the posterior urethral valves, the penile urethra distends like a balloon, as well as the prostatic utricle.

- The severe oligohydramnios is a sign of the precocity and gravity of the lesions. Babies are born with multiple deformities and malformations, especially pulmonary hypoplasia and Potter's facies. Both of these are due to external compression secondary to oligohydramnios and an enlarged bladder.<sup>32,33,38</sup>

When oligohydramnios occurs before 16 weeks of gestational age, it prevents pulmonary development since it does not allow evolution beyond the canalicular stage. Experimental studies have shown that severe oligohydramnios that is sustained



**Fig. 7:** Complete prune-belly syndrome showing abnormalities in the diaphragm with a thoracic herniation of Bochdaleck. The kidneys are usually dysplastic, cystic, hypoplastic, or with hydronephrosis



**Fig. 8:** 2D, Doppler and 3D (arrows) of a megacystis in a 13 weeks gestation

for two weeks prior to week 25, is associated with neonatal mortality that is greater than 90%.<sup>34,35</sup>

- Musculoskeletal (20-50%): Arthrogryposis, absence of limbs, amputations, anomalies of the ribs,<sup>37</sup> hypoplasia of lower limbs, hemimelia, anotia, clubfeet,<sup>2,3</sup> absence of fingers, polydactyly, pectum excavatum or pectum carinatum, scoliosis,<sup>37</sup> thoracic anomalies, congenital hip luxation, vertical talus, myelomeningocele, pubic diastasis,<sup>2</sup> and absence of sacrum.<sup>38</sup>
- Cardiovascular (10% cardiac): Single umbilical cord artery,<sup>3</sup> hepatic and splenic aneurysms,<sup>14</sup> persistence of patent ductus arteriosus, atrial and interventricular septal defects, tetralogy of Fallot.<sup>32,40,41</sup>
- Gastrointestinal (30-50%): Absence of liver, spleen, pancreas, mesocolon, imperforate anus,<sup>3,38,42</sup> intestinal malrotation and malfixation in 30% of cases,<sup>2,42</sup> volvulus, atresias and stenosis (especially of colon), anal and intestinal atresias, persistence of cloaca,<sup>2</sup> tracheoesophageal fistulas, ascitis, visceromegaly or Beckwith-Wiedemann syndrome<sup>38</sup> (Fig. 7).
- Central nervous system: Craniosynostosis, microcephaly, hydrocephaly<sup>3</sup>
- Pulmonary: Cystic adenomatoid malformation.<sup>38</sup>
- Chromosomopathies:<sup>1,42</sup>
  - Trisomy 18<sup>43</sup>
  - Trisomy 13<sup>44</sup>
  - Trisomy 21, frequent<sup>45</sup>
  - 45 XO, rare<sup>1,38</sup>

## OUR CASES

We have carried out a retrospective ultrasonographic study of 15 cases to compare the sensibility of 2D with 3D/4D using different modes (inverse mode, TUI, VOCAL). The only

prospective part is that we are aware of the follow-up and evolution of the images up to the end of gestation. We report our final results because they differ from reports in the world literature.

Our work nevertheless represents one of the largest series in the world literature about PBS and PUV ultrasound characteristics, especially referring to our comparative descriptive observational study between 2D and 3D/4D ultrasonography of these entities. Over the past 10 years, we have made an early prenatal diagnosis of 15 cases presented in Table 1.

Ten cases were diagnosed before week 18. This show that megacystis is very frequent, appears early in pregnancy and easy to diagnose (Fig. 8).

In three cases that were seen previously, the malformation was not visible until after the 18th week, which suggests that the pathogenesis may not only be an obstructive process, but rather a progressive stenosis of the PUV (Fig. 9). Only two had a keyhole sign for which reason we cannot rule out PBS.

Neither is it possible to differentiate, as is mentioned,<sup>31</sup> bladder walls that are thicker or thinner. All bladder walls are thin, as is the case with abdominal walls. The only characteristic that varies is the shape, more or less stretched in some cases.

Our earliest case was seen at 10 weeks and 3 days. It resulted from an IVF-ET case and for this reason we knew the exact date of ovulation and embryo transfer. It is the earliest case described (Fig. 10). Observe that oligohydramnios is not seen.

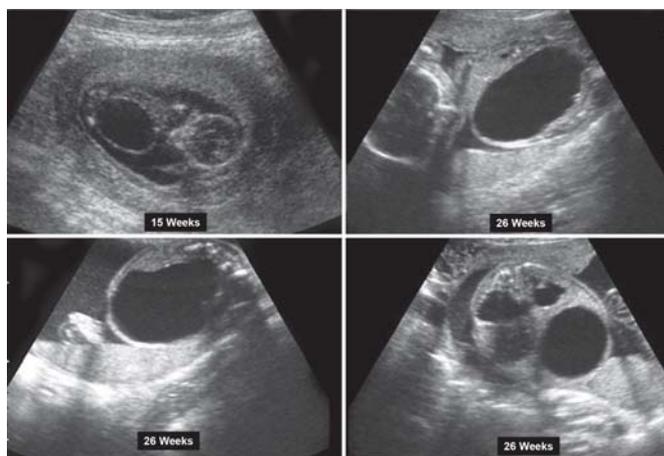
Oligohydramnios was present in nine of our cases. The more advanced the gestation, the more common the presence of oligohydramnios becomes (Fig. 11).

We did not observe abnormal growth parameters (i.e. CRL, BPD, etc.) in any of our cases and neither did we observe any

**Table 1:** Prune-belly syndrome; prenatal ultrasound characteristics and outcome

Case	Week	CRL	BPD	AF	NT	Size	Keyhole	Malf	Obitus	Karyo.	Others
1	10 + 3	33	24.1	NR	0.6	31	Yes	No	11 + 3/s	XY	IVF-ET
2	13 + 3	74	30.6	NR	0.9	28	Yes	No	14 + 4/s	XY	
3	13 + 4	76	31.6	O	1.2	56	Yes	No	13 + 5/s	Unknown	Ovo receptor
4	14 + 3	79	32.0	O	0.0	42	Yes	No	14 + 4/ab	XY	
5	14 + 4	78	32.3	NR	1.6	37	No	No	14 + 6/ab	XY	
6	15 + 1	86	36.0	NR	1.0	38	No	No	17 + 1/s	XY	
7	15 + 4	92	46.0	O	—	67	Yes	Yes	16 + 1/s	XY	Lung, kidney, diaphragm
8	18 + 1	—	44.8	O	—	43	Yes	Yes	18 + 2/ab	XY	Kidney
9	20 + 2	—	44.8	O	—	43	Yes	Yes	22 + 1/ab	XY	Kidney
10	21 + 1	—	56.3	O	—	28	No	Yes	22 + 1/ab	XY	NR since 18 weeks, kidney
11	22 + 3	—	59.6	O	—	26	No	Yes	24 + 1/s	XY	Normal since 18 weeks, kidney, spina bifida
12	26 + 0	—	69.9	NR	—	56	Yes	Yes	28 + 0/s	XY	Normal since 22 weeks, Kidney
13	10 + 1	31	19.2	NR	10	27	No	No	10 + 3/s	XY	
14	13 + 5	78	32.3	O	2.7	33	No	No	13 + 5/s	XY	Ovo receptor
15	24 + 2	—	62.4	O	—	44	Yes	Yes	25 + 5/s	XY	Kidney intestines amniotic band

W – week of gestation at diagnosis; CRL – crown rump length in mm; BPD – biparietal diameter; AF – amniotic fluid (NR – normal, O – oligoamnion); NT – nuchal translucency in mm; S – tumor size in mm; K – Keyhole; M – other malformations; Obitus – week and type: ab – induced abortion, s – spontaneous abortion

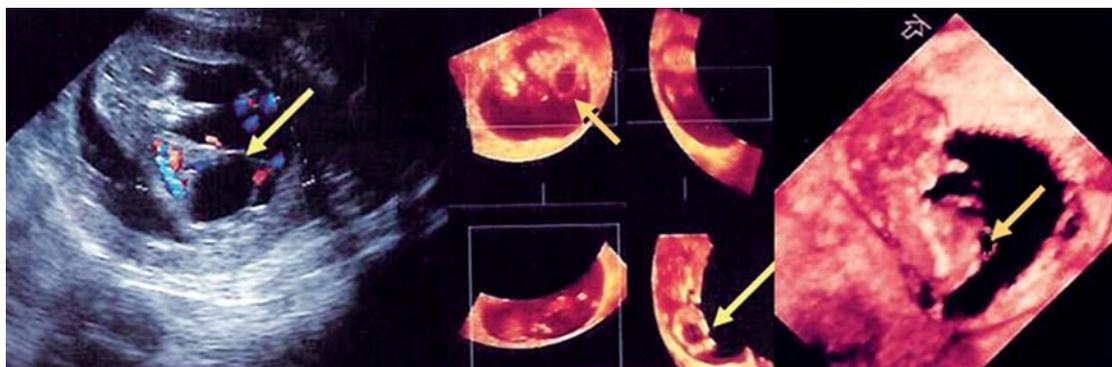


**Fig. 9:** Different forms of megacystis in cases diagnosed at more advanced gestational ages

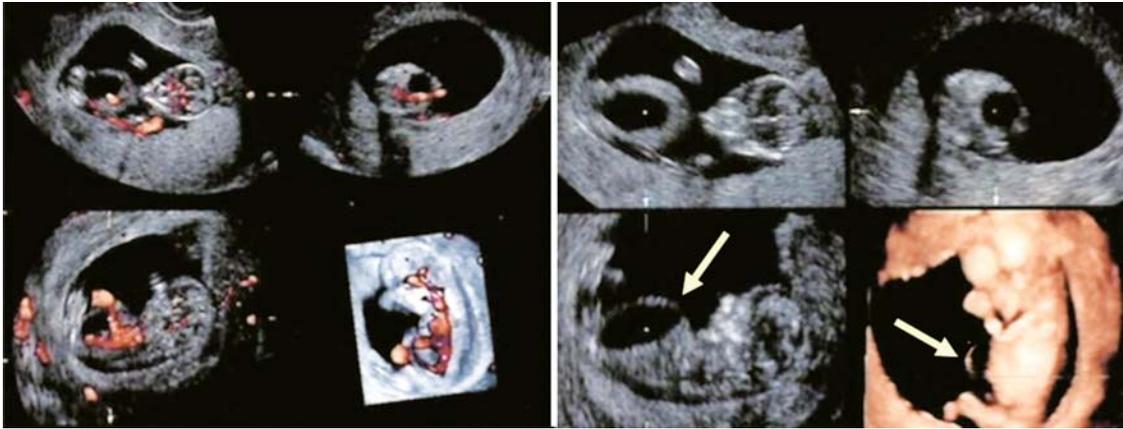
relationship with nuchal translucency width. The karyotype of 14 of our cases was 46XY. We do not know the karyotype of one of our cases because it was aborted in another hospital.

Prognosis in our series was dire. There was intrauterine fetal death in 10 cases and the remaining five cases were aborted. There are two very important data:

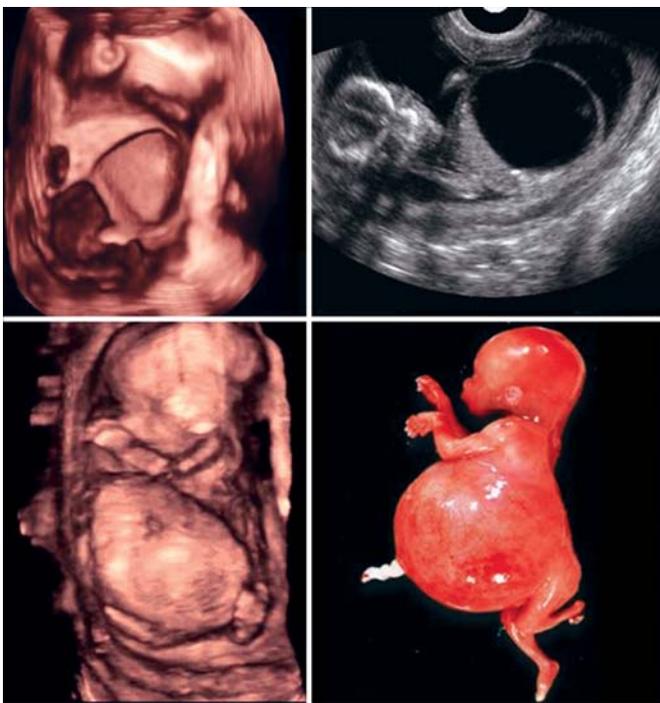
1. Seven cases had other associated abnormalities, among which urethral and renal anomalies were prominent in all cases. There was one case with absence of diaphragm, one amniotic band syndrome, one case of pulmonary hypoplasia, and one case of spina bifida. There was no relationship with presence or absence of a keyhole sign. The cases with associated malformations were the ones diagnosed at more advanced gestational ages. This suggests that a more thorough examination of cases that were aborted at an earlier



**Fig. 10:** Our earliest case of prune-belly which was diagnosed at 10 weeks and 3 days. Megacystis can be seen with 2D and 3D orthogonal planes as well as with 4D surface rendering. There is no oligohydramnios



**Fig. 11:** Two early cases of megacystis seen with 2D, Doppler, and 3D surface rendering. Neither of these has oligohydramnios. At these gestational ages it is difficult to see the keyhole sign

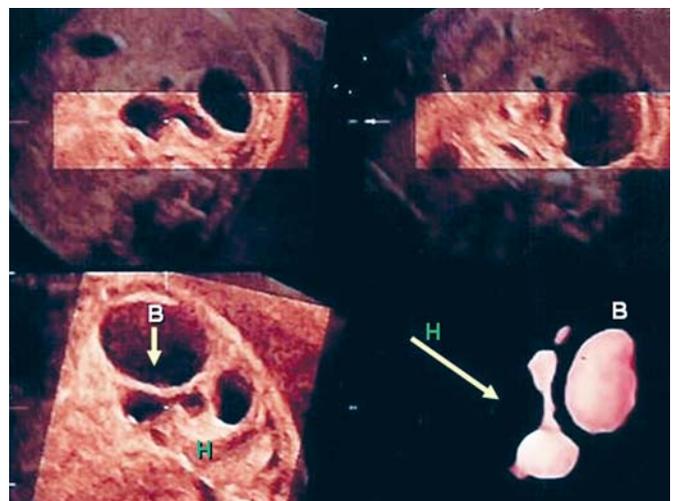


**Fig. 12:** Enormous megacystis with severe pulmonary hypoplasia without oligohydramnios. 3D/4D image and macroscopic image of an early case of prune-belly syndrome (15 weeks + 4 days). The combination of 2D and 3D imaging is extraordinarily valuable to establish diagnosis and prognosis. Observe the tumor, the distention of the abdominal wall which is devoid of musculature, and pulmonary hypoplasia. The images obtained show intrauterine characteristics identical to those obtained following an induced abortion

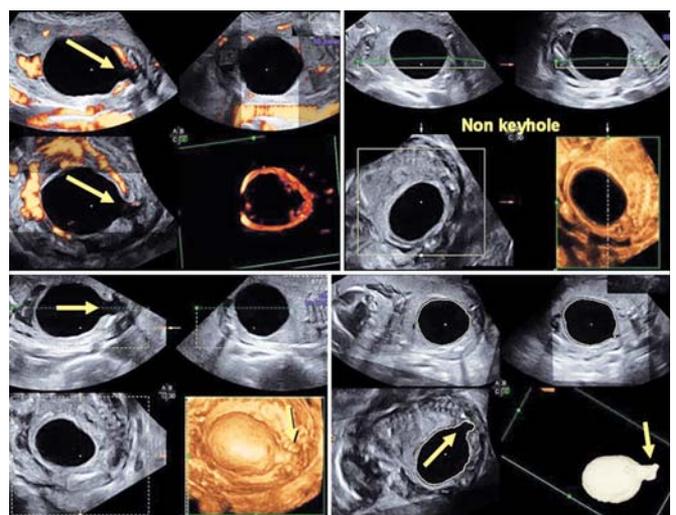
gestational age may have shown one or more associated malformations (Fig. 12).

2. All our cases were initially diagnosed as PBS. Nevertheless, the retrospective ultrasound review revealed a keyhole sign in nine of 15 cases, for which reason they should be classified as PUV cases. Prognosis was not different. Five of the nine cases had other associated malformations. In these cases, 4D modes, TUI and VOCAL, were very helpful and important diagnostic tools (Figs 13 to 15).

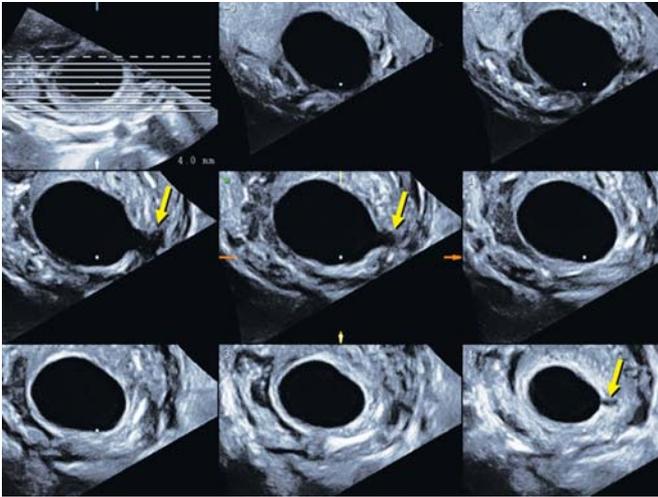
The inverse 4D mode was of exceptional diagnostic value in these cases (Fig. 13).



**Fig. 13:** Inverse 4D mode US. Hydronephrosis and hydroureter are seen. The yellow arrow shows how the megacystis (B – Bladder) has dilated the entire ureter (H – hydroureter) and as a consequence, liquid collections that correspond to renal cysts appear



**Fig. 14:** Multiplanar 3D and VOCAL modes. Upper left, one case with and one without the keyhole sign. With 2D and Doppler the vessels separated by the megacystis are observed. In the lower images, the keyhole sign as seen with 4D and with VOCAL mode. These last two modes are very helpful for establishing a definitive diagnosis as accurately as possible



**Fig. 15:** Tomographic ultrasound imaging (TUI) is also of extraordinary diagnostic help. The possibility of obtaining images that are separated by only millimeters and at different angles, allows much clearer observation of the keyhole sign. The arrows show that this sign appears only at certain slice levels. The keyhole sign could easily be missed without this mode

## DIFFERENTIAL DIAGNOSIS

When an abnormal abdominal protrusion is seen before the 14th week of gestation,<sup>7-9</sup> one must basically consider the following:

- PBS
- PUV, undoubtedly the most frequent cause
- Urethral atresia
- Megacystic microcolon intestinal hypoperistalsis syndrome (MMIHS), of very rare occurrence.<sup>57</sup>
- Urethral diaphragm, penile urethral abnormalities (including stenosis), atresia or multiple urethral lumens.<sup>1</sup> But it has also been noted that obstructive features occur without a demonstrable obstructive lesion. Intermittent obstruction attributed to a flap-like valve created by incompetence of the bladder neck has been demonstrated histologically in prune-belly syndrome cases.<sup>1</sup>

The typical findings in PUV are a male fetus with bilateral hydronephrosis and hydroureter, megacystis, and dilated posterior urethra (keyhole sign), along with thickening of the bladder wall. The penile urethra is of normal caliber, but the prostatic urethra is ballooned out or distended (keyhole sign), frequently with distention of the prostatic utricle (utricle prostaticus) and thickening of the bladder neck. When the obstructive lesion is in the distal portion of the urethra, the most proximal penile urethra is dilated and flaccid.<sup>38</sup> In these fetuses, the observed increase in bladder muscular tissue supports the clinical observation that these bladders can generate considerable internal pressure to the extent that they can secondarily cause injury to the ureters and to the kidneys.

On the other hand, newborn babies with PBS frequently have poor bladder refill with low internal pressure in bladders with scant contractility. When there is MMIHS, there is distention without any pressure and lack of spontaneous urination.<sup>56</sup>

In theory, most cases would develop as urinary tract obstruction leading to marked bladder distention, hydronephrosis, and occasionally to urinary ascitis. There may be in fact three distinct types of PBS. Although these types may result in identical phenotypic appearance, one type may result primarily from dysplastic musculature, and two types may result from bladder obstruction with resultant abdominal distention<sup>27</sup> (Fig. 16).

*Type I:* PUV are mucosal folds extending anteroinferiorly from the caudal aspect of the verumontanum (colliculus seminalis), often fusing anteriorly at a lower level. They are derived from the *plicae colliculi*.

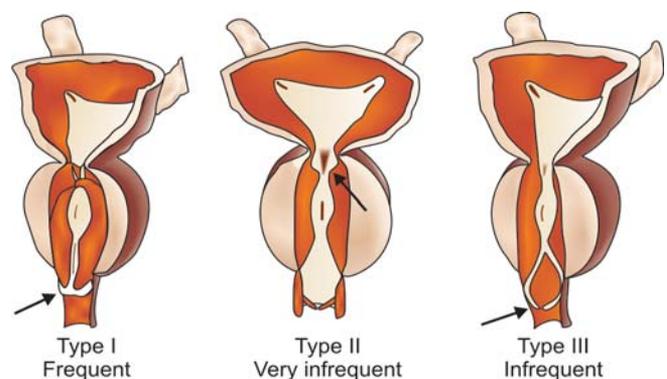
*Type II:* PUV are mucosal folds extending anterosuperiorly from the verumontanum toward the bladder neck.

*Type III:* PUV are disk-like membranes located below the verumontanum in two different ways:

1. In the first type, the valve extends from the verumontanum distally.
2. In the second type, the valve extends from the verumontanum towards the bladder neck.

Prune-belly can be confused with megacystis secondary to posterior urethral valves and with urethral atresia with which it is also associated.<sup>3,23</sup> When there is severe megacystis in the first trimester, urethral atresia is the most common diagnosis. It can be associated with prune-belly, and in these cases prognosis is worse and differential diagnosis becomes much more difficult.<sup>3</sup> PBS has been identified as “plum belly” syndrome when there is complete urethral obstruction.<sup>31</sup>

Megacystic microcolon intestinal hypoperistalsis syndrome, or Berdon’s syndrome,<sup>46</sup> is a rare congenital defect of unknown origin that is characterized by nonobstructive bladder distention, hydronephrosis, hydroureter, intestinal hypoperistalsis, and microcolon. It appears to be a colonic and vesical neurologic myopathy with degenerative vacuolar signs and an increase in connective tissue in the smooth muscle of these tissues. This leads to a decreased, nonobstructive tone in the bladder that results in the absence of spontaneous micturition. The intestines are poorly developed, stenotic or atretic.<sup>47-49</sup> In these cases amniotic fluid is normal. This syndrome is much more frequent



**Fig. 16:** Types of posterior urethral valves (Young, 1919)

**Table 2:** Megacystis: Differential diagnosis

<i>Prune-belly</i>	<i>PUV</i>	<i>MMIHS</i>
Stricture entire length of urethra No keyhole sign	Keyhole sign	No keyhole sign
Bladder with thin wall	Bladder with thick rounded wall (Donut like)	Bladder with thin wall
Oligohydramnios	Oligohydramnios	Normal amniotic fluid
Union between the bladder and urethra dilated (Wine glass or funnel shape)	Union between bladder and urethra hypertrophied	Normal union between the bladder and the urethra
Male (97%)	Male (100%)	Female (80%)
Infrequent	Frequent	Rare
<i>In utero</i> diagnosis	Diagnosis <i>in utero</i> , neonatal, childhood, or as an adult	<i>In utero</i> diagnosis

in females (4 to 1). The few cases described are from necropsy findings. Differential diagnosis with PUV is therefore difficult, and more so with PBS with the exception that in cases of MMIHS amniotic fluid is normal and the majority of cases occur in females. However, the cases are so rare that we have only found five reports in the literature, all diagnosed as megacystis with definitive diagnosis confirmed only following delivery and necropsy<sup>47-49</sup> (Table 2).

Undoubtedly, many of the cases described as PBS are PUV, MMIHS, or vice-versa. Other investigators<sup>37,38</sup> have arrived at identical conclusions by doing histologic studies of prune-belly and PUV cases. Phenotypically PBS cases with an increase in bladder muscular mass would be really PUV cases. Nevertheless, the possible diagnostic error would be scarcely significant since prognosis at these early gestational ages are equally ominous,<sup>38</sup> although it is probably not as grim for newborn babies.

We must keep in mind that there are other fetal abdominal cysts:

- Small bowel atresia. It has a polycystic image, very similar to what is seen in renal cases. The volume of amniotic fluid is normal, the urinary bladder fills regularly, and if we are able to see the kidneys, they have a normal appearance.
- Ovarian cyst. It is a single cyst in the lower pelvis. The amniotic fluid volume is normal and there is never oligohydramnios. The kidneys and ureters are normal. The fetus is obviously female.
- Omphalocele. Ultrasonographically, it is an extra-abdominal tumor covered with a fine, almost transparent membrane that is much thinner than the abdominal wall and with similar characteristics to the amnion. The umbilical cord inserts at the apex of the tumor. The entire sac and its contents float in the amniotic fluid.
- Gastroschisis. This is a real evisceration. It usually appears after the 14th week of gestation. Unlike the omphalocele, intestinal loops float freely in the amniotic fluid without an enveloping membrane as is seen in omphaloceles.
- Imperforate anus. Unlike the above mentioned cases, the cystic image is grayish, has somewhat irregular borders, may be of different sizes.

- Mesenteric cyst. It is extraordinarily rare and difficult to diagnose. It presents as an abdominal cyst with both kidneys having a normal appearance. The bladder fills and empties normally and all the digestive organs are otherwise normal. The diagnosis is usually one of exclusions.
- Duodenal atresia. This malformation produces the typical “double bubble” image.
- Liver cysts,<sup>50</sup> fetal ascitis,<sup>51,52</sup> amniotic band syndrome,<sup>8,53</sup> perirenal urinary extravasation, presacrococcygeal teratoma, urethral duplication, megalourethra, anterior urethral diverticulum, syringocele, urethral hypoplasia, urinary retention, and ectopic ureterocele.<sup>63</sup>

**PROGNOSIS**

Prognosis is established based on six ultrasonographic parameters:

- 1st The degree of obstruction (complete or incomplete)
- 2nd The level of the obstruction. Severe renal insufficiency is rarely seen with high-level obstructive uropathies, but lower-level obstructive uropathies are usually severe or lethal if their natural evolution is allowed to progress. Mid-level obstructive uropathies are of unpredictable behavior
- 3rd Duration of the obstruction
- 4th The precocity of its manifestation
- 5th The laterality of the renal lesion
- 6th The degree of pulmonary hypoplasia.

We suggest that it is important to distinguish between both entities. The etiologic diagnostic accuracy of the process can be a predictive factor for success of intrauterine therapy in postnatal life. True prune-belly syndrome seems to have a better long-term prognosis.

When the anomalies appear early and the obstructive problem is severe, following hyperdistention of urethra, bladder, ureters, and finally the kidneys, hydronephrosis appears and this in turn prevents development of glomeruli and their union

with proximal tubules. Renal function will be severely affected and altered.

This situation will lead to severe oligohydramnios and absence of fetal micturition. At the same time severe pulmonary problems may appear. Prognosis in these cases is always extremely poor.

In any of these cases survival depends on renal function. For cases with bilateral renal dysplasia prognosis is guarded. If renal function is preserved, the prognosis is good when early surgery is done in these cases.

The information provided by ultrasonographic evaluation of the fetal kidneys is decisive in determining antenatal and postnatal prognosis. We can encounter three situations:

1. Renal scanning reveals the existence of cortical cysts. There is in addition severe oligohydramnios. We have in this case severe and irreversible renal dysplasia.
2. Renal studies reveal a good delimitation of corticomedullary differentiation and amniotic fluid is normal. Renal function is well preserved in this case.
3. The renal parenchyma has discrete alterations with poorly differentiated cortical cystic structures. The amniotic fluid volume diminishes in subsequent serial studies. More thorough evaluation of renal function to determine the degree of compromise should be advised. Biochemical studies of fetal or newborn urine will provide important prognostic data.

Regarding future pregnancies, the risk of recurrence is unknown, but is considered to be very low. Familial recurrence has been described suggesting, at least in some cases, a type of genetic inheritance.<sup>54</sup> Global mortality is at least 60% only during the first postpartum week.<sup>15</sup>

## INTRAUTERINE MANAGEMENT

The only solution prior to the 24th week of gestation is the placing of a vesicoamniotic shunt<sup>55</sup> which can improve survival if:

1. There are no other malformations.
2. There is a normal karyotype, and
3. There is renal function.

These conditions are not present in 75% of cases.

It is recommended that decompression be carried out prior to the 20th week of gestation, since earlier the treatment administered less will be the degree of irreversible kidney damage.<sup>56</sup> It has been shown in animal models that decompression at an early gestational age was able to restore renal and pulmonary function. The value of vesicoamniotic shunt (VAS) in humans remains controversial. There is a high rate of complications inherent in the technique and a high rate of renal failure in subsequent infancy.<sup>57</sup> Up to 33% needed dialysis and transplantation.<sup>56</sup>

The VAS procedure seeks two objectives:

1. Restoration of an adequate volume of amniotic fluid to avoid pulmonary hypoplasia and Potter's sequence.

2. Decompression of the urinary tract to avoid progression to irreversible renal dysplasia.

Therefore, the VAS procedure is fundamentally indicated for obstructive uropathies that are associated with oligohydramnios.

After the 26th week of gestation, cesarean section or Nd-YAG laser ablation of the posterior urethral valves by the anterograde route with cystoscopy-urethroscopy following cystostomy.<sup>58-62</sup> The results, however, are not encouraging. For the time being, this procedure is reserved for complicated cases of obstructive uropathy where performance of a conventional shunt is not possible.

## SUMMARY

With an ultrasound finding of megacystis and oligohydramnios, it should be determined to which of the two etiologic groups the case belongs:

- a. Obstructive pathology (i.e. PUV, anterior urethral valves, urethral atresia, urethral agenesis, urethral meatus stenosis).
- b. Nonobstructive primary pathology (i.e. PBS, congenital hypoperistaltism syndrome).

Intrauterine differential diagnosis is not always possible due to the precocious appearance of megabladder in some cases and to the presence of oligohydramnios which makes ultrasound evaluation very difficult.

Classically, the megabladder in cases of PUV is described with thickened bladder walls (due to hypertrophy that is secondary to the obstruction) and with the presence of the so called "keyhole sign" that corresponds to the dilatation of the proximal urethra. Bladder wall thickening is difficult to appreciate.

Therefore, the only important ultrasonographic distinguishing finding that is truly important is the keyhole sign, which would indicate the presence of PUV. Unfortunately, PBS can on occasions be associated with this pathology.

Conversely, if there is no associated obstructive process, the bladder wall is usually not thickened in cases of PBS. The typical PBS is considered to be secondary to a connective tissue and smooth muscle abnormality,<sup>60</sup> which causes bladder distention and result in oligohydramnios. These fetuses are defined as "true PBS cases" as a different group from fetuses with complete urethral obstruction, which are identified as "plum belly" cases.

## REFERENCES

1. Popek EJ, Tyson RW, Miller GJ, Caldwell SA. Prostate development in prune-belly syndrome (PBS) and posterior urethral valves (PUV): Etiology of PBS-lower urinary tract obstruction or primary mesenchymal defect? *Pediatr Pathol* 1991;11:1-29.
2. Herman TE, Siegel MJ. Prune-belly syndrome. *J Perinatol* 2009;29:69-71.
3. Chen L, Cai A, Wang X, Wang B, Li J. Two- and three-dimensional prenatal sonographic diagnosis of prune-belly syndrome. *J Clin Ultrasound* 2010;38:279-82.

4. Balaji K, Patil A, Townes P, et al. Concordant prune-belly syndrome in monozygotic twins. *Urology* 2000;55:949-53.
5. Baird PA, MacDonald EC. An epidemiologic study of congenital malformations of the anterior abdominal wall in more than half a million consecutive live births. *Am J Hum Genet* 1981;33:470-78.
6. Papantoniou N, Papoutsis D, Daskalakis G, Chatzipapas J, Sindos M, Papaspirou I, Mesogitis S, Antsaklis A. Prenatal diagnosis of Prune-belly syndrome at 14 weeks of gestation: Case report and review of literature. *J Maternal-Fetal Neonatal Med* 2010;early online. 1-5.
7. Bonilla Musoles F, Machado LE, Osborne N. 3D-4D ultrasound of the new Millennium. Panamericana (Ed). Madrid 2000.
8. Bonilla Musoles F, Machado LE 3D-4D ultrasound in Obstetrics. Panamericana (Ed). Madrid 2005.
9. Hoshino T, Ihara Y, Shirane H. Prenatal diagnosis of prune-belly syndrome at 12 weeks of pregnancy: Case report and review of the literature. *Ultrasound Obstet Gynecol* 1998;12:362-66.
10. Frydman M, Magen RE, Mohandas TK, et al. Chromosome abnormalities in infants with prune-belly anomaly: Association with trisomy 18. *Am J Med Genet* 1983;15:145-48.
11. Buyse ML. Birth Defects Encyclopedia. Blackwell Scientific Publ. Center for Birth Defects Information Services, Inc. Massachusetts 1990.
12. Wheatley JM, Stephens FD, Hutson JM. Prune-belly syndrome: Ongoing controversies regarding pathogenesis and management. *Semin Pediatr Surg* 1996;5:95-106.
13. Woods AG, Brandon TH. Prune-belly syndrome. A focused physical assessment *Adv Neonatal Care* 2007(7);132-43.
14. Alhawsawi AM, Aljiffry M, Walsh MJ, Peltekian K, Molinari M. Hepatic artery aneurysm associated with prune-belly syndrome: A case report and review of the literature. *J Surg Educ* 2009; 66:43-47.
15. Druschel CM. A descriptive study of prune-belly in New York State, 1983 to 1989. *Arch Pediatr Adolesc Med* 1995;149:70-76.
16. Fröhlich, F *Der Mangel der Muskeln. Insbesondere der Seitenbauchmuskeln.* Dissertation: Würzburg 1839.
17. Parker R. Absence of abdominal muscles in an infant. *Trans Clin Soc.* 1875, 28, 2001-03.
18. Eagle JF, Barrett GS. Congenital deficiency of abdominal musculature with associated genitourinary abnormalities: A syndrome. Report of 9 cases. *Pediatrics* 1950;6:721-36.
19. Obrinsky W. Agenesis of abdominal muscles with associated malformation of the genitourinary tract: A clinical syndrome. *Am J Dis Child* 1949;77:362-73.
20. Nunn IN, Stephens FD. A composite anomaly of the abdominal wall, urinary system and testes. *J Urol* 1961;86:782-94.
21. Freedman AL, Johnson MK, Smith CA, Gonzalez R, Evans MI. Long-term outcome in children after antenatal intervention for obstructive uropathies. *Lancet* 1999;354:374-77.
22. Guvenc M, Guvenc H, Aygun D, Yalcin O, Gaydinc YC, Soyflu F. Prune-belly syndrome associated with omphalocele in a female newborn. *J Pediatr Surg* 1995;30:896-97.
23. Yiee J, Wilcox D. Abnormalities of the fetal bladder. *Semin Fetal Neonatal Med* 2008;13:164-70.
24. Kraim J, Ben Brahim I, Jouini H, Ben Brahim Y, Chatti S, Falfould A. Prune-belly syndrome early prenatal diagnosis and management. *Tunis Med* 2006;84:458-61.
25. Feldman S, Hassan S, Kramer RL, Kasperski SS, Evans MI, Johnson MP. Amnioinfusion in the evaluation of fetal obstructive uropathy. The effects of antibiotic prophylaxis on complication rates. *Fetal Diagn Ther* 1999;14:172-75.
26. Bonilla Musoles F, Machado LE, Osborne N. Gastrointestinal tract and internal abdominal wall. In: Kurjak A, Azumendi G: *Fetus in Three Dimensions. Imaging, Embriology and Fetoscopy.* Healthcare. Abingdon, UK 2006. pp 287-308.
27. Bonilla Musoles F, Raga F, Machado LE, Bonilla F Jr, Osborne N. News on 3D-4D Sonographic applications in the diagnosis of fetal malformations. In: *Donald School Textbook of Ultrasound in Obstetrics and Gynecology.* (2nd ed). Kurjak A, Chervenak FA (Eds). 2008, 640-61.
28. Bonilla Musoles F, Machado LE, Raga F, Castillo Jc, Osborne N, Bonilla F Jr, Machado F. 3D/4D US In Fetal Malformations. Part Three: Second trimester. skeletal disorders, thoracic, abdominal, kidney and other malformations. In: *Current Topics on Fetal 3D/4D Ultrasound.* Hata T, Kurjak A, Kozuma S. Bentham Science Publishers. Busum Holanda, 2009 ISSN: 978-1-60805-019-2,87-133.
29. Huang WC, Yang SH, Yang JM. Two- and three-dimensional ultrasonographic findings in urethral stenosis with bladder wall trabeculation: case report. *Ultrasound Obstet Gynecol* 2006;27, 697-700.
30. Kalache KD, Bamberg C, Proquitte H, Sarioglu N, Lebek H, Esser T. Three-dimensional multi-slice view: New prospects for evaluation of congenital anomalies in the fetus. *J Ultrasound Med* 2006, 25, 1041-50.
31. Johnson MR, Fredman AL. Fetal uropathy. *Curr. Opin. Obst. Gynecol.* 1999;11:185-94.
32. Megan M, Bogan MD, Holly E, Arnold MD, Kenneth E, Greer MD. Prune-Belly syndrome in two children and review of the literature. *Pediatr Dermatol* 2006;23:324-45.
33. Bogart MM, Arnold HE, Greer KE. Prune-belly syndrome in two children and review of the literature . *Pediatr. Dermatol* 2006;23:342-45.
34. Kilbride HW, Yeasty J, Thibeault DW. Defining limits of survival:Lethal pulmonary hypoplasia after midtrimester premature rupture of membranes. *Am J Obstet Gynecol* 1996; 75:675-81.
35. Laudy JA, Wladimiroff JW. The fetal lung:1. Developmental aspects. *Ultrasound Obstet Gynecol* 2000;16:284-90.
36. Laudy JA, Wladimiroff JW. The fetal lung: 2. Pulmonary hypoplasia. *Ultrasound Obstet Gynecol* 2000;16:482-94.
37. Workman S, Kogan BA. Fetal bladder histology in posterior urethral valves and prune-belly syndrome. *J Urol* 1990;144:337-39.
38. Pagon RA, Smith DW, Shepard TH. Urethral obstruction malformation complex: A cause of abdominal muscle deficiency and the "prune-belly". *J Pediatr* 1979;94:900-06.
39. Macpherson RI, Leithiser RE, Gordon L, Turner WR. Posterior Urethral valves: An update and review. *RadioGraphics* 1986;6:753-91.
40. Drugan A, Zador IE, Bhatia RK, Sacks AJ, Evans MI. First trimester diagnosis and early in utero treatment of obstructive uropathy. *Acta Obstet Gynecol Scand* 1989;68:645-49.
41. Yoshida M, Matsumura M, Shintaku Y, Yura Y, Kanamori T, Matsushita K, Nonogaki T, Hayashi M, Tauchi K. Prenatally diagnosed female prune-belly syndrome associated with tetralogy of Fallot. *Gynecol Obstet Invest* 1995;39:141-44.
42. Cianciosi A, Mancini F, Busacchi P, Carletti A, De Aloysio D, Battaglia C. Increased amniotic fluid volume associated with cloacal and renal anomalies. *J Ultrasound Med* 2006;25:1085-90.
43. Nivelon Chevallier A, Feldman JP, Justrabo E, Turc Carel C. Trisomy 18 and prune-belly syndrome. *J Genet Hum* 1985 33:469-74.

44. Cazorla E, Ruiz F, Abad A, Monleon J. Prune-belly syndrome: Early antenatal diagnosis. *Eur J Obstet Gynecol Reprod Biol* 1997;72:31-33.
45. Metwalley KA, Farghalley HS, Abd-Elshayed AA. Prune-belly syndrome in an Egyptian infant with Down syndrome: A case report. *J Med Case Reports*. 2008;2:322-25.
46. White SM, Chamberlain P, Hitchcock R, Sullivan PB, Boyd PA. Megacystis-microcolon-intestinal hypoperistalsis syndrome: The difficulties with antenatal diagnosis. Case report and review of the literature. *Prenat Diagn* 2000;20:697-700.
47. Beltran JR, Serrano A, Coronel B, Dominguez C, Estornell F, Garcia Ibarra F. Síndrome de Berdon (megavejiga, microcolon, hipoperistalsis). Presentación de nuestros casos. *Acta Urol. Esp.* 2004;28:405-08.
48. Fujimoto C, Bartholomew ML. Just images: Obstetrics. *Donald School J. Ultrasound Obstet Gynecol* 2010;4:73-88.
49. Yamamoto H, Sera Y, Ikeda S, Terakura H, Yoshida M. Giant liver cyst in a fetus with prune-belly syndrome. *Pediatr Surg Int* 1994;9:417-18.
50. Hirose R, Suita S, Taguchi T, Kukita J, Satoh S, Koyanagi T, Nakano H. Prune-belly syndrome in a female, complicated by intestinal malrotation after successful antenatal treatment of hydrops fetalis. *J Pediatr Surg* 1995;30:1373-75.
51. Freid S, Appelman Z, Caspi B. The origin of ascites in prune-belly syndrome: Early sonographic evidence(2). *Prenat Diagn* 1995;15:876-77
52. Chen CP, Liu FF, Jan SW, Wang KG, Lan CC. First report of distal obstructive uropathy and prune-belly syndrome in an infant with amniotic band syndrome. *Am J Perinatol* 1997;14:31-33.
53. Callen P. Ultrasonography in Obstetrics and Gynecology. Fetal syndromes. Prune-belly syndrome (5th ed). Chapter 5. 2008: 164-65.
54. Bonilla-Musoles F, Pellicer A, Benedito D, Sánchez-Peña JM, Vázquez R, Ramírez JV. Tratamiento médico y quirúrgico del feto intraútero. *Rev. Españ. Obstet. Ginecol.* 1984;43:381-415.
55. Leeners B, Sauer I, Schefels J, Cotarelo C, Funk A. Prune-belly syndrome: Therapeutic options including in utero placement of vesicoamniotic shunt. *J Clin Ultrasound* 2000;28:500-06.
56. Vanderheyden T, Kumar S, Fish NM. Fetal renal impairment. *Seminars in Neonatology* 2003;8:279-89.
57. Woodhouse CR, Kellet MJ, Williams DL. Minimal surgical interference in the prune-belly syndrome. *Brit J Urol* 1979;51: 59-62.
58. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PR. Fetal hydrolaparoscopy and endoscopic cystotomy in complicated cases of lower urinary tract obstruction. *Am J Obstet Gynecol* 2000;183:324-33.
59. Danzer F, Sydorak RM, Harrison MR, Albanese CT. Minimal access fetal surgery. *Eur J Obstet Gynecol Reprod Biol* 2003; 108:3-13.
60. Freedman AL, Qureshi F, Shapiro EM, Lepor H, Jacques SM, Evans MI. Smooth muscle development in the obstructed fetal bladder. *Urology* 1997;49:104-07.
61. Romero R, Pilu G, Jeanty P, Hobbins JC. Prenatal diagnosis of congenital anomalies: Prune-belly syndrome. In: Romero R, Pilu G, Jeanty P, Ghidini A, Hobbins JC, editors. *Prenatal diagnosis of congenital anomalies*. Norwalk, CT: Connecticut, Appleton & Lange, 1988;289-90.
62. Woodward PJ, Kennedy A, Sohaey R, Byrne JLB, Oh KY, Puchalski MD. Diagnostic imaging obstetrics. Chapter 9. Salt Lake City, USA: Amirsys Inc., 2005;49-52.
63. Kajbafzadeh A. Congenital urethral anomalies in boys. Part I: Posterior urethral Urol J 2005;2:59-78.