SONOGRAPHIC DIAGNOSIS OF FETAL UROPATHY

EMBRYOLOGY

The urinary and genital systems develop from a common mesodermal ridge on the posterior abdominal wall. The 3 primordia of the definitive kidney (pronephros, meosonephros, and metanephros) develop sequentially; not only in time, but also in location. The pronephros arises cranially, the mesonephros in the mid-abdomen, and the metanephros caudally. The metanephros, or permanent kidney, begins to develop when the ureteric bud connects with the metanephros. The ureteric bud divides into two diverticula that eventually become major and minor calyces, as well as the remainder of the collecting system. The metanephric cap differentiates into the functioning units of the kidney or nephrons. The functioning nephrons continue to increase in number during prenatal development. Additional nephrons do not form after birth. As noted above, the metanephros is located within the pelvis. The apparent "ascent" of the kidneys is due to the rapid growth of the lumbar and sacral regions. Because of its change in location, the kidneys are vascularized by successively higher branches from the aorta.

The cloaca is separated by the urorectal septum into the urogenital sinus and anorectal canal. By week 7 the ureters open separately and directly into the bladder that has evolved from the urogenital sinus.

The production of urine begins by the 8th menstrual week as a plasma filtrate. The onset of renal tubular function is around 14 weeks. Urinary output is 5 ml/hr at 20 weeks' gestation and increases to 50 ml/hr by 40 weeks[1].

Between 10-14 weeks' gestation an enlarged bladder with a diameter of 7-15 mm (Fig. 1) is associated with a 25% risk of aneuploidy. When the bladder diameter is > 15 mm, progressive obstructive uropathy invariably results[2].

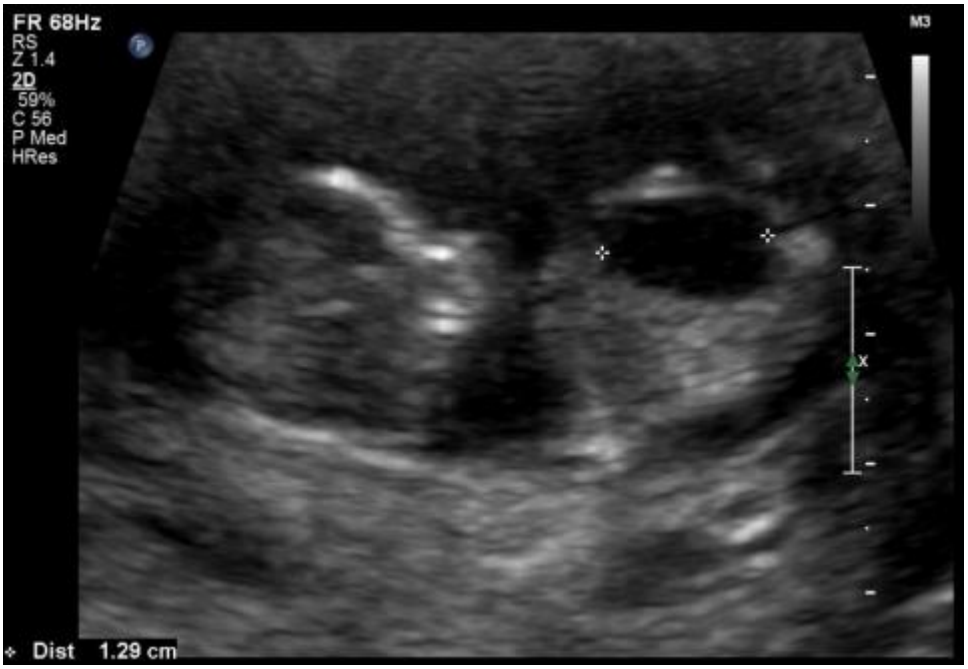

Figure 1. 11 week gestation with a 13 mm bladder (between graticules). Click for larger image.

PYELECTASIS

Pyelectasis refers to isolated dilatation of the renal pelves (Fig. 2) and is likely physiologic in origin, but may be due to ureteropelvic junction obstruction or reflux.

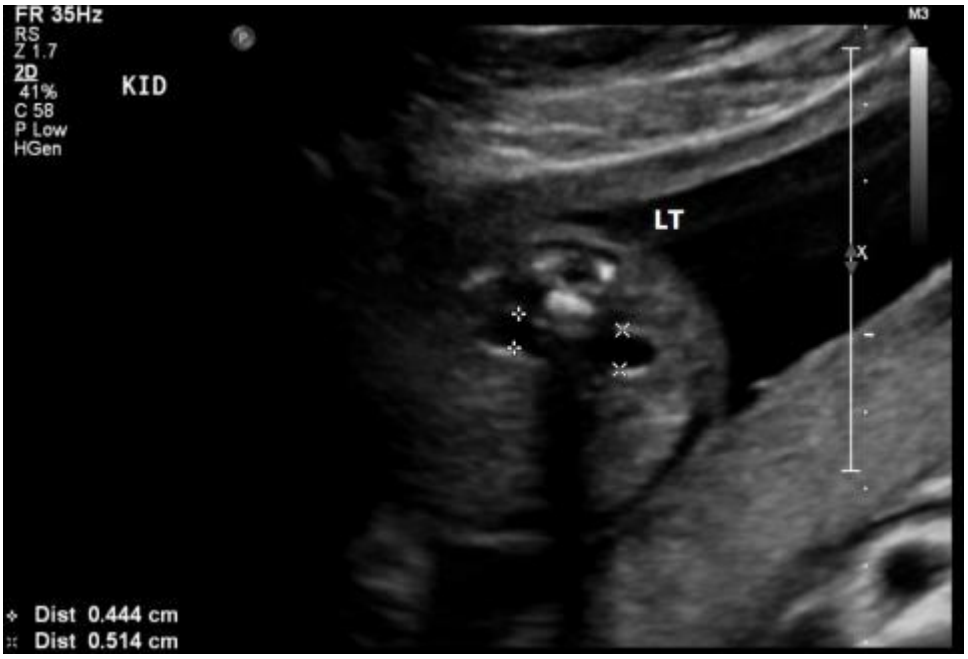

Figure 2. Left (LT) pyelectasis (5.1 mm) at 18 weeks' gestation. Click for larger image.

Transient upper urinary tract dilatation may be due to the slow canalization of the excretory system or delayed maturation of the urological junctions[3].

The incidence of 2nd trimester pyelectasis varies with one's definition of a dilated renal pelvis, but is generally between 2%[3,4] and 4.6%[5]. The average diameter of the renal pelvis is gestational age dependent. Therefore, it is a continuous, rather than categorical, variable. As a result, any single value for 2nd trimester pyelectasis is a compromise and will have a poor sensitivity and specificity for predicting subsequent neonatal obstruction. Dilatation into the caliceal system (Fig. 3) may also be physiologic, but increases the likelihood of obstruction or reflux.

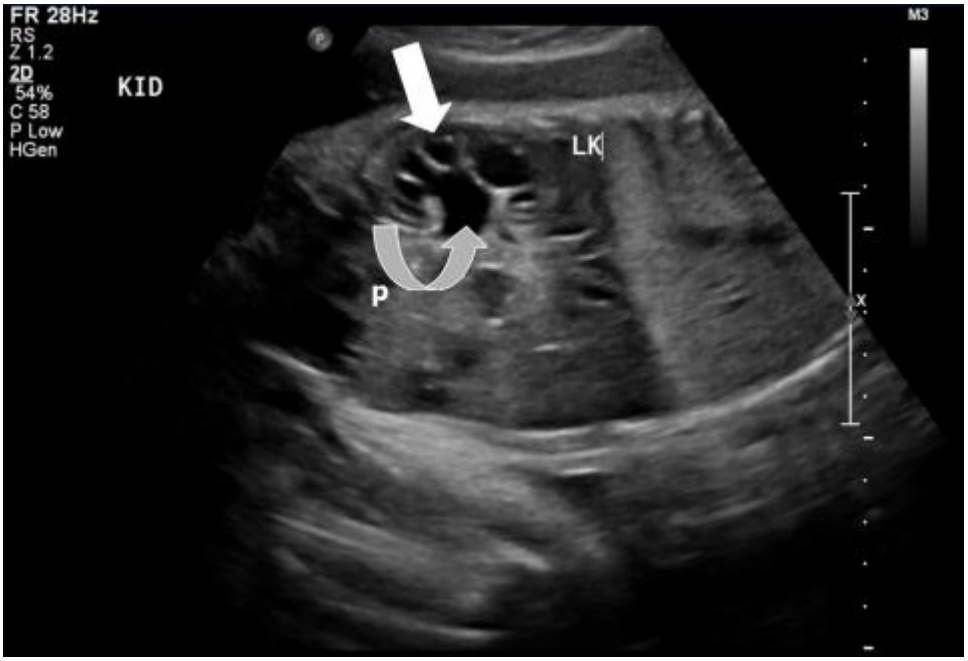

Figure 3. Left (LK) pyelectasis (p) and caliectasis (arrow). Click for larger image.

In the 2nd trimester the antero-posterior dimension of the renal pelvis in autopsied kidneys of fetus without renal disease is 3.61 mm and 3.51 mm on the right, and 3.58 mm and 3.41 mm on the left for males and females, respectively[6].

Several authors have concluded that a renal pelvis transverse dimension in the 2nd trimester > 5 mm[2,6,7] and > 7 mm in the 3rd trimester[2,8] require follow up for possible hypdronephrosis. While a lower threshold would be more sensitive in detecting postnatal obstruction, the false positive rate is higher. As one would expect, the likelihood of postnatal pathology increases from mild (11.9%) to moderate (45.1%) to severe (84.3%) pyelectasis. In some cases of severe obstruction, renal pelvis dilatation is not evident until after 24 weeks' gestation[9].

The current definitions of pyelectasis in the 2nd and 3rd trimester are outlined in Table I. During the antenatal period approximately 80% of pyelectasis is mild, 15% moderate, and 5% severe1. After the detection of 2nd trimester pyelectasis, a follow up examination in the 3rd trimester with a stable or reduced renal pelvis diameter generally indicates eventual spontaneous resolution. Neonatal resolution of persistent antenatal pyelectasis is felt to be secondary to resolution of ureteral kinks and/or folds[1].

Maternal hydration influences fetal urine flow rate and renal pelvis diameter. Hence, the ingestion of 48 ounces of water prior to an examination results in an increased prevalence of pyelectasis[10].

Fetal bladder distension can affect the size of the renal pelves. If pyelectasis is detected, a repeat measurement with an empty fetal bladder should be obtained to confirm the finding. In one study 53% of fetuses with pyelectasis and a full bladder had normal renal pelves with bladder emptying[11].

Pyelectasis tends to resolve or improve in 80% of cases[1].

The male/female ratio for fetal pyelectasis is 2:1[12,13,14]. The presence of fetal pyelectasis in one pregnancy increases the likelihood of detection in a subsequent sibling[1].

The delineation of pyelectasis into three groups (Table I) can help with the development of a neonatal management scheme. Infants with severe renal pelvis dilatation in the 3rd trimester should undergo postnatal diagnostic testing and indicated treatment. While patients with moderate pyelectasis have a high prevalence of uropathy, they rarely require surgery and pyelectasis may resolve spontaneously. The majority of patients with mild pyelectasis do not have significant neonatal findings. The latter two groups (mild and moderate) can be followed for recurrent urinary tract infections or progressive pyelectasis as an indicator that additional testing is required[1,15].

Table I. Definitions of Pylelectasis

	Second Trimester	Third Trimester
Mild	5.0-6.9mm	7.0-8.9mm
Moderate	7.0-8.9mm	9.0-14.9mm
Severe	>10mm	>15mm

Derived from Nguyen HT et al. J Pediatr Urol 2010;6:212.

Calyceal dilatation is an important additional finding with pyelectasis that significantly increases the likelihodd of postnatal surgery and renal compromise[5]. Moderate to severe calyceal dilatation is clearly abnormal and will generally required neonatal surgery[16].

A 2nd trimester antero-posterior renal pelvis diameter > 4.0 mm (Fig. 2) is considered a soft sonographic marker for trisomy 21[17,18]. Despite the higher prevalence in males, gender does not affect the association with fetal trisomies. Hence, counseling with respect to the risk of trimsomy can be gendered indepent[14].

URETEROPELVIC JUNCTION OBSTRUCTION (UPJ)

Ureteropelvic junction obstruction has an incidence of 1 in 2,000 livebirths[19,20.] 90% of cases are unilateral; males are more commonly affected. Extraluminal UPJ is due to a fibrous band or an aberrant vessel. Hence, the secondary obstruction may be intermittent. Luminal causes of UPJ are more common and are due to a build up of collagen and muscular fibers at the posterior urethral junction[3]. The presence of a valve or ureteral polyp are examples of intraluminal etiologies of UPJ.

25% of UPJ obstructions have other associated urologic abnormalities, including renal dysplasia, renal agenesis, and vesico-ureteral reflux[21]. 12% may have extra-renal anomalies[22].

Hydronephrosis by definition indicates renal obstruction. Hence, this term can only be used with certainty after an appropriate neonatal evaluation. As the severity of obstruction worsens, the calyces change in appearance from dilated (Fig. 3) to rounded (Fig. 4) to absent (Fig. 5)[16].

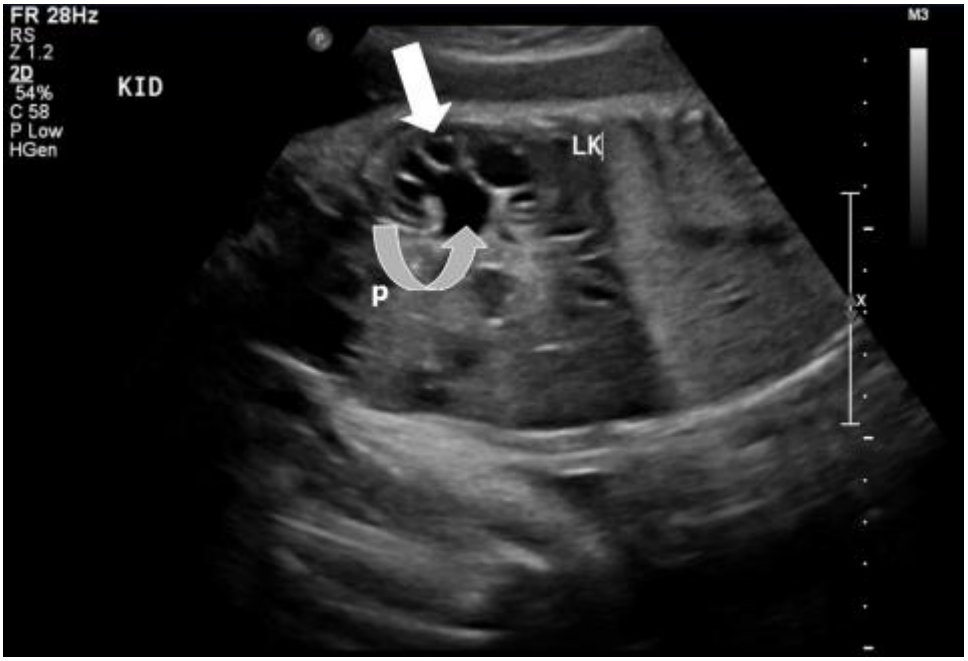

Figure 3. Left (LT) pyelectasis (5.1 mm) at 18 weeks' gestation. Click for larger image.

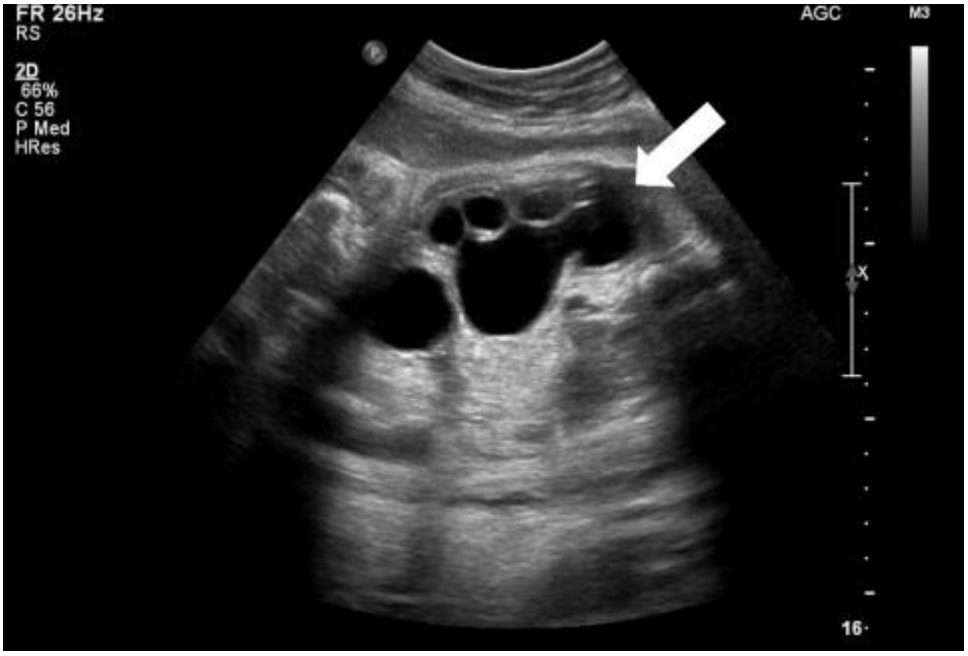

Figure 4. Rounded calyces (arrow) with UPJ obstruction. Click for larger image.

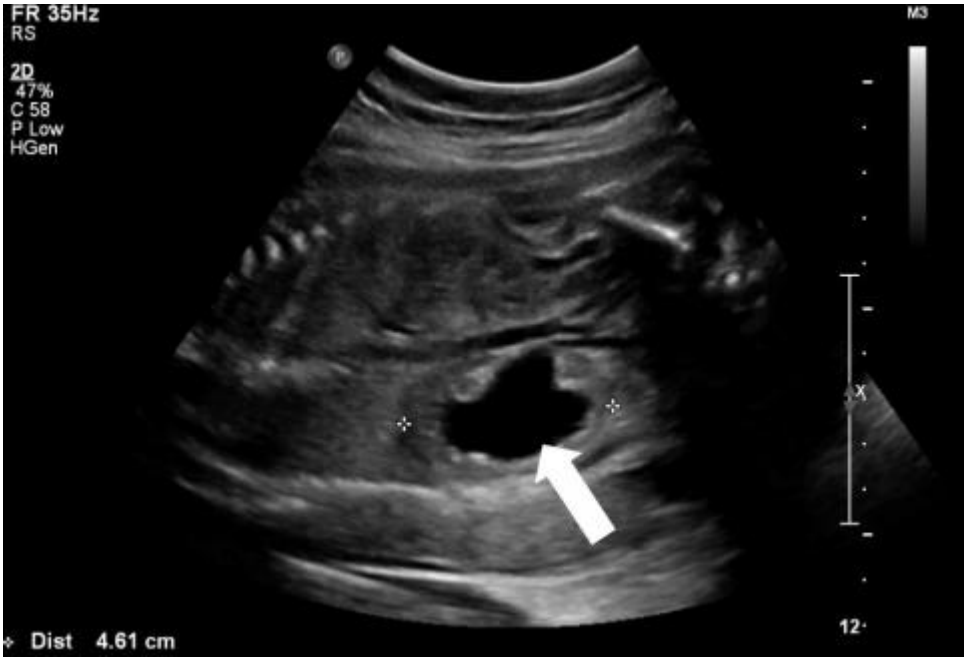

Figure 5. Loss of calyceal shape (arrow) with severe UPJ obstruction. Click for larger image.

A renal parenchyma thickness < 3 mm would be considered significantly thinned (Fig. 6). This does not always equate with poor renal function. With the relief of an obstruction in the neonatal period, the parenchymal dimension may return to a more normal diameter and renal function may also be normal[5].

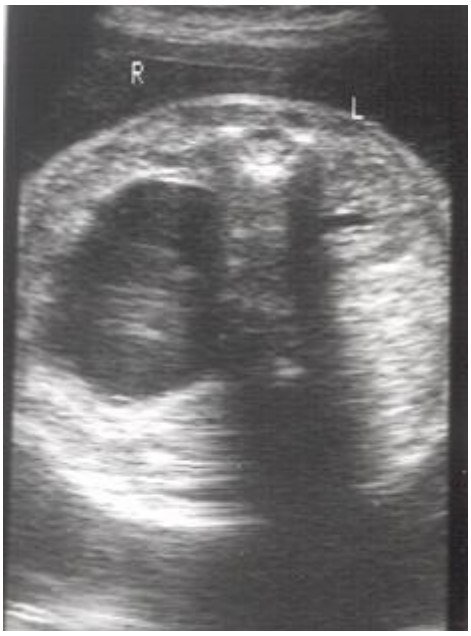

Figure 6. There is a complete loss of renal architecture of the right kidney (R) and the parenchyma is < 3 mm. Click for larger image.

When upper tract obstruction is gradual or of later onset, urine production is unaffected as long as the compliance of the collecting system can adapt to the increased urinary volume. If the obstruction continues, there is increased peristalsis, decreased compliance and hypertrophy of the collecting system. Eventually a renal affect from obstruction is demonstrated by a reduction in growth and an increase in fibrosis. If the obstruction occurs early, small dysplastic kidneys result without the adaptive processes outlined above[3,19]. When the obstruction is unilateral and occurs early enough in gestation, there is compensatory hypertrophy of the contralateral kidney[23].

HYDROURETER

Possible etiologies of a hydroureter (Fig. 7) include a megaureter, ureterocele, severe reflux, vesico-ureteral obstruction, and posterior urethral valves.

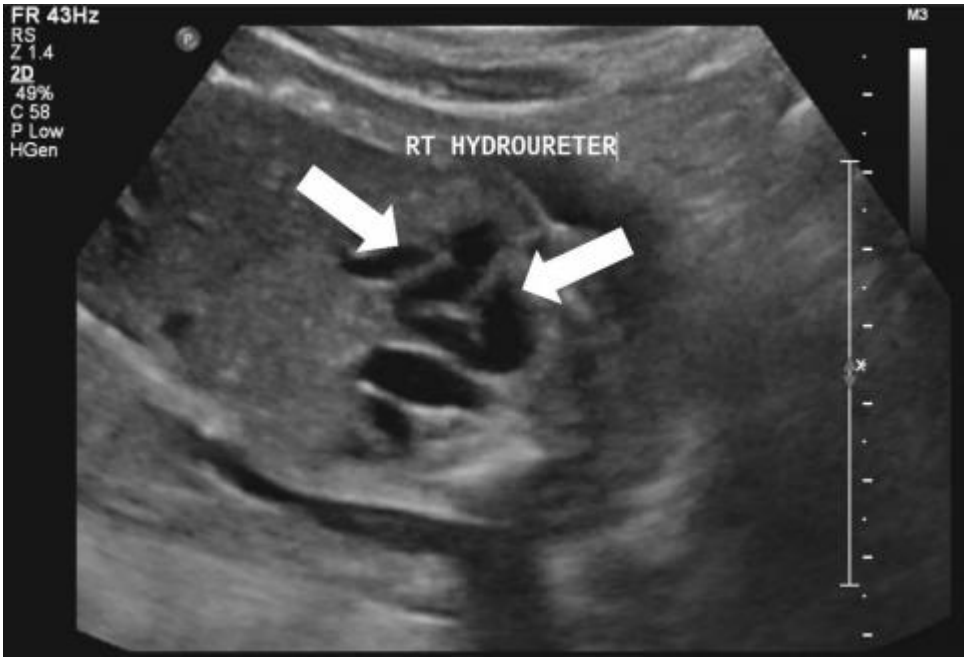

Figure 7. Right hydroureter (arrows). Click for larger image.

A megaureter is due to aperistalsis in the distal ureter. The incidence of primary megaureter is 1/6,500 livebirths. 25% of cases are bilateral. 16% of cases have additional anomalies, primarily within the urinary tract. Pelvic kidneys, vesicoureteral reflux and UPJ obstruction have all been described with megaureter[3]. Spontaneous resolution during the neonatal period has been reported[1,24].

A ureterocele (Fig. 8) is a cystic dilatation of the distal intravesical portion of the ureter. Usually the ureterocele is at the orifice draining the upper pole of a duplex kidney. The severity of the obstruction by the ureterocele determines the extent of ureteral and renal obstruction. In some cases, the obstruction can result in renal dysplasia of the lower pole of the kidney.

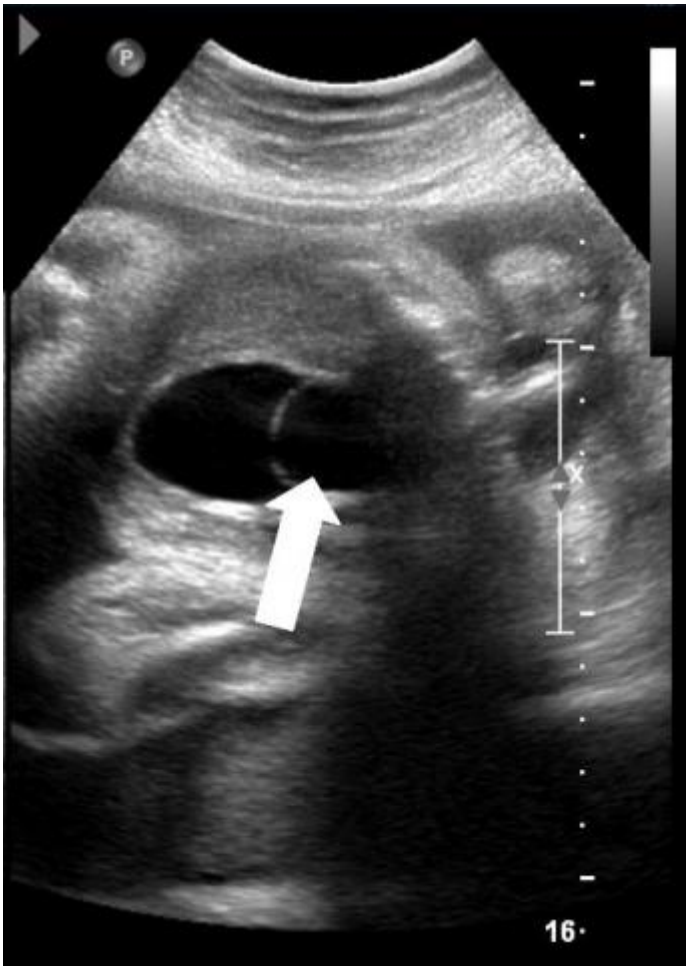

Figure 8. Ureterocele (arrow). Click for larger image.

Vesicoureteral reflux (VUR) is graded as outlined on Table II[25]. Only grade 3 or grade 4 reflux results in hydroureter. Spontaneous resolution of VUR occurs in 69.1% with grade I, 55.7% with grade II, and 49.1% of patients with grade III[26]. Pyelectasis, therefore, has a poor sensitivity for the detection of reflux. Bladder dilatation may be a transient finding with severe reflux and is, therefore, sometimes confused with early posterior urethral valves. VUR is associated with other urinary malformations, including unilateral renal agenesis, multicystic kidneys and posterior urethral valves[3]. VUR occurs in up to 46% of asymptomatic siblings of children with clinically confirmed reflux[27]. Vesicoureteral reflux (VUR) is graded as outlined on Table II[25]. Only grade 3 or grade 4 reflux results in hydroureter. Spontaneous resolution of VUR occurs in 69.1% with grade I, 55.7% with grade II, and 49.1% of patients with grade III[26]. Pyelectasis, therefore, has a poor sensitivity for the detection of reflux. Bladder dilatation may be a transient finding with severe reflux and is, therefore, sometimes confused with early posterior urethral valves. VUR is associated with other urinary malformations, including unilateral renal agenesis, multicystic kidneys and posterior urethral valves[3]. VUR occurs in up to 46% of asymptomatic siblings of children with clinically confirmed reflux[27].

Table II. Classification of vesicoureteral reflux.

Grade	Description
I	Reflux into non-dilated ureter
II	Reflux into kidney without ureteral dilatation
III	Mild/moderate ureteral dilatation, renal calyces with minimal blunting
IV	Dilatation renal pelvis with moderate ureteral tortuosity

V Marked urteral dilatation and tortuosity; dilated calyces, loss of papillary impressions
Derived from Lebowitz RL et al. Pediatr Radiol 1985;15:105.

LOWER URINARY TRACT OBSTRUCTION (LUTO)

Bladder outlet obstruction is caused by stenosis, atresia, or a web across the distal urethra. The earlier the diagnosis is made, the more likely it is due to atresia[28]. A distended proximal urethra (Fig. 9) at the site of obstruction is specific for posterior urethral valves, but is not present in every case. With progressive obstruction the bladder wall thickens to > 3 mm (Fig. 10). In cases of a posterior urethral web, the increasing bladder pressure required to move urine past the web will, in some cases, rupture the web, resulting in a spontaneous cure of the obstruction.

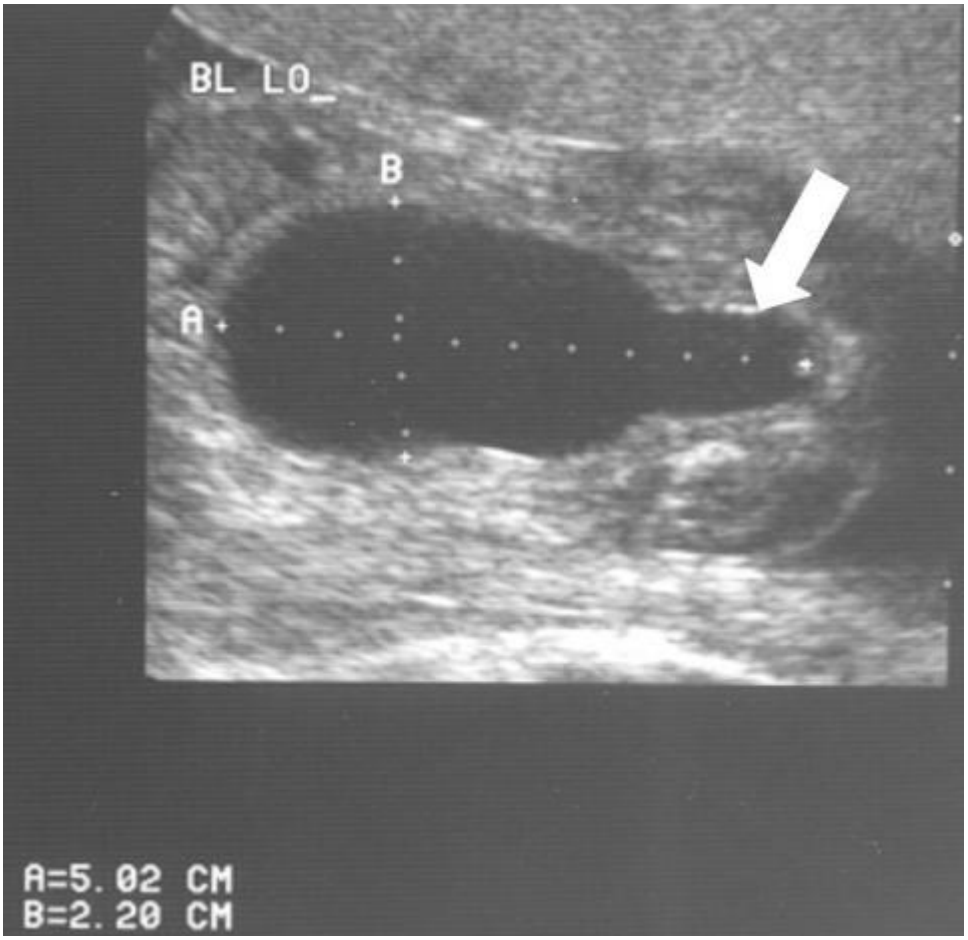

Figure 9. Posterior urethral valves - dilated proximal urethra (arrow). Click for larger image.

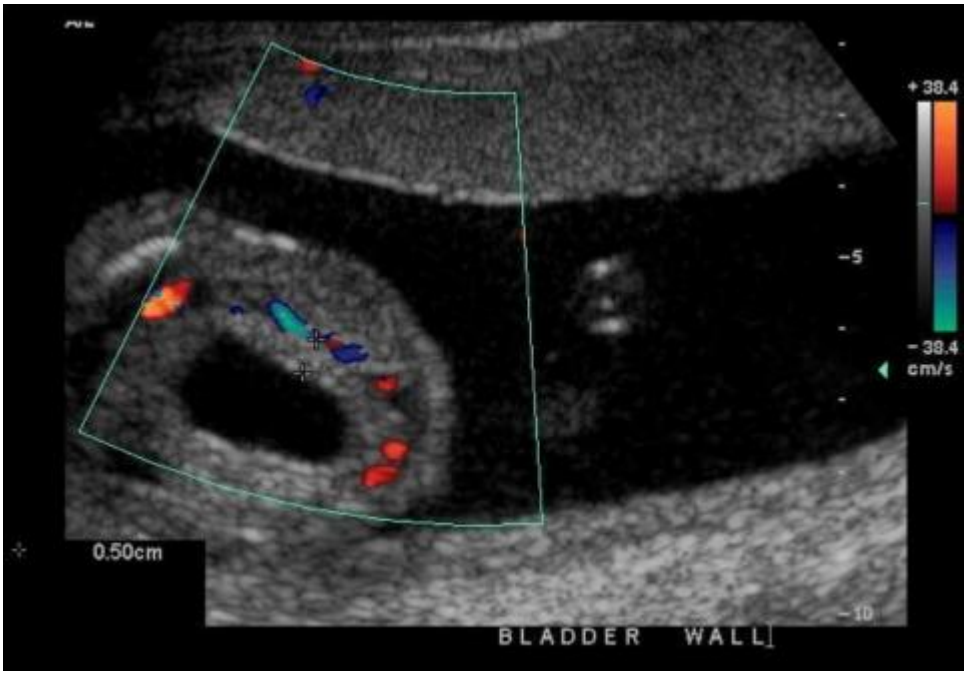

Figure 10. Thickened bladder wall (between graticules) due to posterior urethral valves. Click for larger image.

In males, posterior urethral valves is the most common cause of bladder outlet obstruction. However, in females a persistent cloaca and other complex genitourinary anomalies are more frequently responsible for lower level urinary tract obstruction[29].

An occasional finding associated with bladder outlet obstruction is urinary ascites secondary to bladder disruption[30]. While this is an indication of significant bladder pressure, the reduction of urinary tract pressure may serve to protect remaining renal function. The formation of a urinoma (Fig. 11) is also due to a disruption of the urinary tract in the retroperitoneal space[30]. Since pressure on the kidney persists due the limited space within the urinoma, renal function will continue to be compromised.

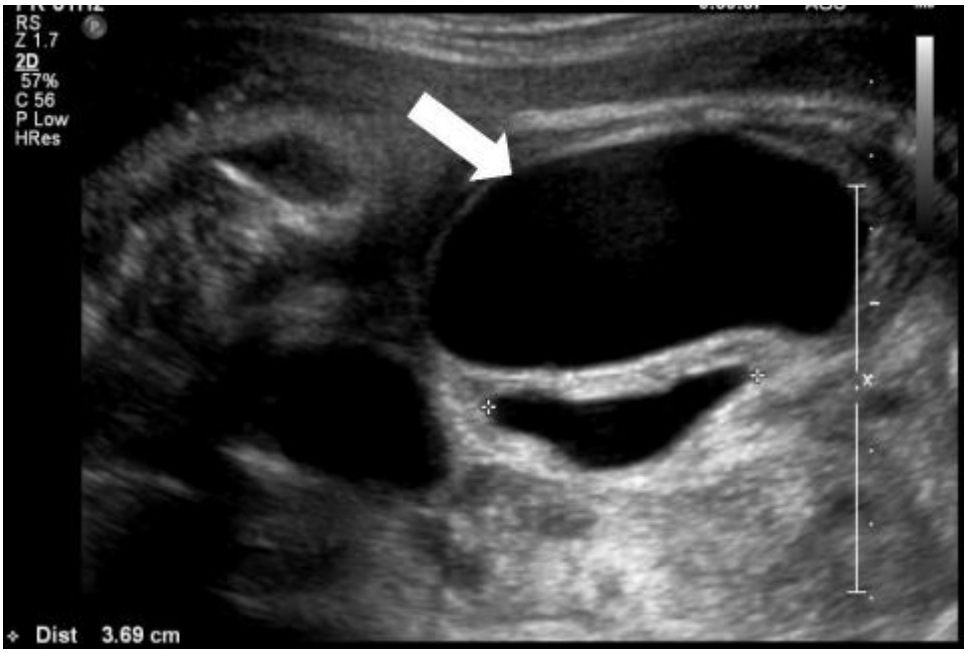

Figure 11. Loss of renal calyces within kidney (graticules) with a urinoma (arrow). Click for larger image.

MANAGEMENT

Once a fetal uropathy has been identified sonographically, management and prognosis are the primary concerns of both the healthcare provider and patient. The upper and middle uropathies may be either unilateral or bilateral. With unilateral lesions, as long as contra-lateral function is preserved, the outlook is generally excellent. When both kidneys are affected by a uropathy, the possibility of in utero therapy and/or timed delivery must be entertained.

A thorough fetal anatomic survey looking for associated congenital anomalies is mandatory before developing a management plan for a diagnosed uropathy[31,32].

A decision regarding fetal karyotyping must be individualized. The reported rate of aneuploidy with LUTO is around 5%[33]. As the number of detectable anomalies increases, so does the risk of a karyotypic abnormality[31]. However, whenever in utero therapy is entertained, karyotyping would seem advisable, as part of a complete evaluation.

Fetal renal function cannot be directly assessed. Since creatinine and uric acid cross the placenta and correlate with maternal concentrations, an assessment of renal function from fetal blood is unreliable. An evaluation of the potential long-term effects of a fetal uropathy utilizes the sonographic assessment of the degree of obstruction, the architectural appearance of the renal parenchyma, amniotic fluid volume and, in isolated cases, fetal urinalysis.

Bilateral renal hyperechogenicity and small cortical cysts are indicative of end-stage renal disease (Fig. 12). Since the progression of renal compromise is on a continuum, the presence of these sonographic markers has a high positive predictive value, but poor sensitivity, for detecting fetal renal failure[34]. Kidneys with a length > 95th centile for gestational age that are not echogenic have a better prognosis[32].

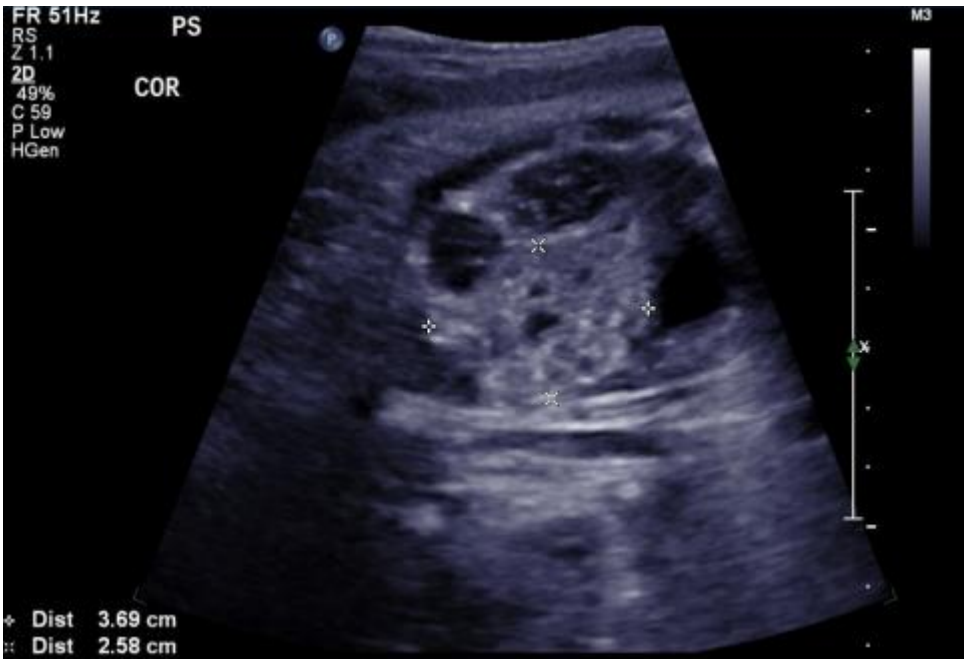

Figure 12. Echogenic kidney (between graticules) secondary to obstruction. Click for larger image.

Amniotic fluid volume is a reflection of total fetal urinary output. Serial amniotic fluid indices can, therefore, assess the progression of renal compromise. Anhydramnios, when 2nd trimester normal amniotic fluid has been previously documented, suggests anuria secondary to renal failure.

While the above sonographic findings correlate with poor postnatal renal function (serum creatinine = 1.2 mg/dl), the relatively wide confidence intervals of any one parameter limits the application of the

information in individual cases[35]. For example, renal dysplasia may be irreversible by the time oligohydramnios is apparent[33].

Prematurity and pulmonary hypoplasia are the principle causes of mortality with LUTO. 95% mortality rates have been reported with early 2nd trimester oligohydramnios and uretheral obstruction[33].

A sampling of fetal urine is reserved for cases of suspected severe outlet obstruction. A normal comparison group has been derived from either normal fetuses prior to termination[36], or fetuses with an obstruction who were subsequently found to have normal renal function as a neonate[37].

Indices of tubular function undergo significant changes as gestational age advances. Fetal urine is isotonic to plasma at less than 20 weeks' gestation. For example, at 16 weeks' gestation a normal urinary sodium approaches 120 mml/L. It is only after approximately 22 weeks' gestation that a urinary sodium of = 100 mEq/L is considered indicative of poor renal tubular function. Chloride concentrations of > 90 mEq/L and osmolality of > 210 mOsm/L are additional urinary findings associated with poor renal function[33].

Fetal serum ?-2 microglobulin levels (an index of glomerular filtration rate) are independent of gestational age. A urinary ?-2 microglobulin > 13 mg/l predicts perinatal death and a level of > 2 mg/l is indicative of postnatal renal failure . Fetuses with a normal urinary sodium, but an elevated beta 2 mircroglobulin are at increased risk for subsequent neonatal renal failure. There is neither an individual analyte, or combination of analytes with a high sensitivity and specifity for detecting poor neonatal renal outcome[34,38.]

Three sequential fetal urinary samples should be obtained at 48-72 hour intervals. The 1st sample empties the sequestered urine from the bladder and the 2nd sample collects urine from the upper urinary tract. The final sample that is used for analysis reflects urine that has been recently produced by the kidneys. Since vesicourethral reflux may be more severe on one side, the extent of renal damage may also vary. There have been reports of unilateral renal dysplasia on one side with a normal functioning kidney on the other side. Hence, in cases where the kidneys appear architecturally dissimilar, renal pelvic sampling has been proposed[38].

Experimental data from the fetal lamb model suggests that bladder shunting in cases of outlet obstruction can prevent the onset of renal dysplasia[39]. Initial attempts to resolve LUTO by open fetal cystostomy were frought with complications and soon abandoned in favor of vesico-amniotic shunting (Fig. 13).

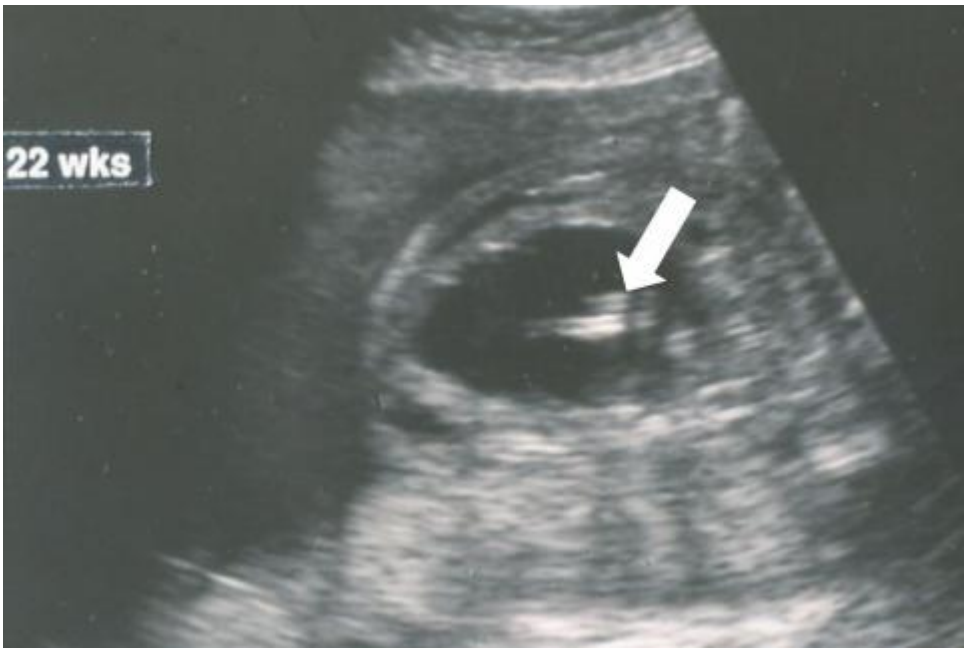

Figure 13. Vesio-amniotic shunt (arrow). The amniotic fluid volume has been restored to normal. Click for larger image.

Morris and co-workers[40] published a protocol-driven systematic review that could not show any benefit of antenatal intervention for preserving normal renal function. While antenatal bladder drainage may improve perinatal survival, there is also a high risk of poor postnatal renal function. After a successful vesico-amniotic shunt, 44% of infants in one study had acceptable renal function and 34% required a renal transplant[33]. Hence, the efficacy of this approach has not been proven in humans[41]. Displacement of a vesico-amniotic shunt occurs in 40% of cases[33].

Fetal procedural morbidity, initiation of pre-term labor, and the potential of fetal demise, mandates that strict guidelines must be followed to ensure that this procedure is only offered in appropriate cases.

The percutaneous shunting in lower urinary tract obstructin (PLUTO) study is a randomized controlled trial comparing in-utero vesico-amniotic shunting with conservative management. Recruitment for this study is closed and the data is being evaluated. Hopefully, the results of the study will provide appropriate guidance for the management of LUTO[42].

More recently, fetal cystoscopy has been introduced in an attempt to improve upon the varying success rates reported with vesico-amniotic shunting associated with catheter dislodgement and clogging. In this technique, an endoscope is introduced into the fetal bladder and directed toward the bladder neck and dilated proximal urethra. Laser fulguration of the valves is performed, permitting the egress of urine through the urethra[43]. Because of the relatively small number of cases to date, a comparison of this procedure with vesico-amniotic shunting cannot, yet, be performed[40].

CONGENITAL MEGALOURETHRA

Dilatation of the penile urethra (Fig. 14) results in a functional obstruction of the lower urinary tract. Congenital megalourethra is due to a deficiency of the corpus cavernosum and/or spongiosum; this is a rare anomaly with only 80 cases reported in the English literature by 2002[45]. Since the urethra lacks support, there is urinary stasis during micturation. Megacystis, bilateral hydroureter, and bilateral hydronephrosis may result. Postnatal surgical correction is possible[44].

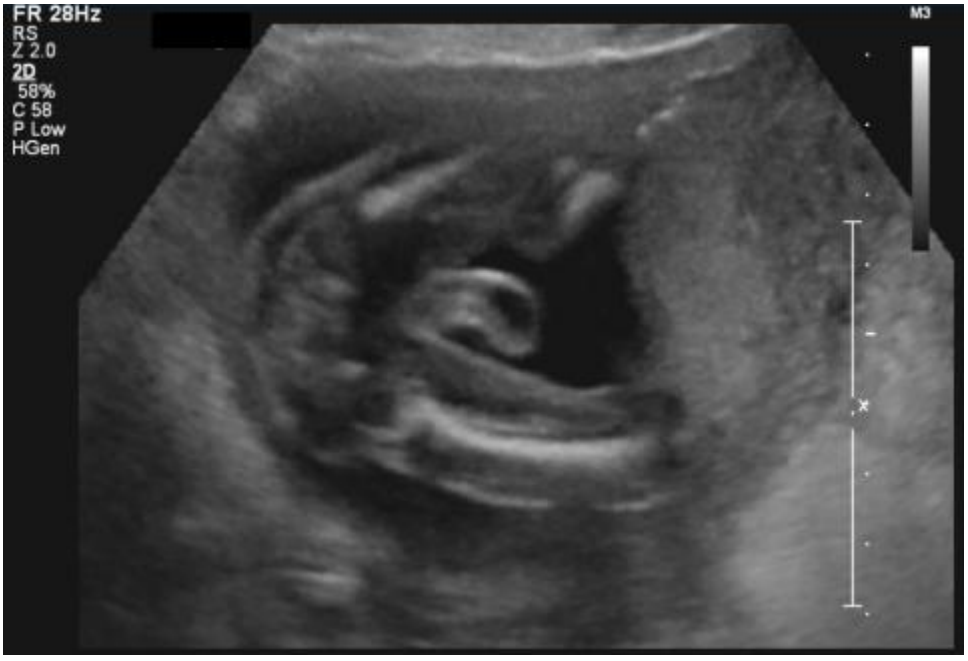

Figure 14. Congenital megalourethra. Click for larger image.

Congenital megalourethra is associated with other genitourinary anomalies, including reflux, renal agenesis and prune belly syndrome[45].

CONCLUSION

Obstructive abnormalities of the urinary tract are the most common anomalies detected on an antenatal ultrasound. Urine production begins at 8 weeks' menstrual age and the earliest detection of obstruction is between 10 and 14 weeks' gestation. The anatomic evolution of the urinary tract over the 1st and 2nd trimesters may result in a temporary obstruction. A systematic prenatal evaluation can result in, not only a correct diagnosis, but also an appropriate managements scheme. In the more severe cases of bilateral obstruction, pre and postnatal evaluation should be individualized in order to optimize long-term renal function.

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