AUA **Update Series** 2020

Lesson 15 Volume 39

Prenatal Urology Diagnoses*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to counsel the family of the unborn child with a suspected urology diagnosis, and recognize and differentiate the most serious conditions that will require tertiary care following delivery, including lower urinary tract obstruction, bladder and/or cloacal exstrophy and spina bifida.

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INTRODUCTION

The identification of congenital urinary tract anomalies is commonplace with the routine use of ultrasound technology in modern prenatal care. **A prenatal urology diagnosis affects approximately 2% to 3% of all pregnancies.**[1] **Based on 2018 birth estimates of 3.7 million births in the United States between 75,000 and 115,000 fetuses are affected annually.**[2] A practicing urologist must be aware of the most common diagnoses so appropriate counsel can be provided to expectant families and treating obstetricians. One must assess the risk for postnatal pathology so that delivery planning and postnatal assessment can be discussed. This Update provides the practicing urologist with the tools to recognize the most common diagnoses, to identify patients at greatest risk for true postnatal pathology and to actively participate in the management of a fetus with a prenatal urology diagnosis.

ULTRASOUND USE, TIMING AND SENSITIVITY

In the last 4 decades rapid expansion of prenatal ultrasound has driven prenatal urology diagnosis. From the mid-1990s to the mid-2000s prenatal ultrasound use doubled in North America.[3] **Moreover, the American College of Obstetrics and Gynecology recommends a minimum of 1 prenatal ultrasound, with optimal timing suggested between 18 and 22 weeks of gestation**.[4] Numerous indications exist for screening ultrasound but identifying major fetal organ anomalies remains the primary goal. **Studies indicate that overall sensitivity of ultrasound for detecting any fetal organ anomaly is 40%, yet the sensitivity of detecting a urology diagnosis approaches 90%**.[5] Thus, prenatal urology diagnoses are more likely to be found than other organ systems.

KEY EVENTS IN FETAL KIDNEY AND BLADDER DEVELOPMENT

When counseling the family of a fetus with a potential urology diagnosis, an appreciation of timing is important. On a basic level, one must know timing of the developmental events that occur in the urinary tract and, while not an exhaustive review of urological embryology, key events of fetal kidney, ureter and bladder development are presented.

The fetal kidney develops from intermediate mesoderm lying laterally on either side of the fetus. In week 3 cranial to caudal folding of the fetus occurs which is an important event for bladder and kidney development. Shortly thereafter enlargement of the intermediate mesoderm forms the urogenital ridge that will give rise to the kidney. During week 3 the 2 precursors to the mature kidney, the primitive pronephros and mesonephros, appear and extend from the cervical region to the sacral region of the embryo. While the pronephros will disappear by week 5, the mesonephros will persist until week 16. In week 4 the nephric (wolffian) ducts appear on each side of the embryo, which give rise to the ureteric bud in week 6. The development of the mature kidney, the metanephros, begins in week 6 with the sacral ureteric bud contacting the metanephric mesenchyme.

As a result of this interaction, extensive branching occurs which will persist until week 32 and leads to the development of a full complement of nephrons. During weeks 6 to 9 the developing kidneys migrate from the sacral region of the embryo to the lumbar region.[6] Fetal urine production begins by 10 weeks of gestation, and the kidneys become visible on sonography by approximately 15 weeks of gestation.[7]

Simultaneously, the bladder develops from the cloacal membrane, a 2-layer structure comprised of endoderm and ectoderm in the sacral end of the fetus. In week 4 the cloacal membrane dilates to become the cloaca. In weeks 5 and 6 the cloaca divides into the anterior urogenital sinus and the posterior anorectal canal. The developing common excretory duct, which arises from the distal portion of the nephric duct, contacts the urogenital sinus in week 6 to form the trigone of the bladder.[6] The urine filled fetal bladder becomes visible on ultrasound by 10 to 14 weeks of gestation.[8] **In the second half of pregnancy following keratinization of the fetal skin, urine comprises a majority of the amniotic fluid.**[9] Fetal survival, lung development and renal function depend on the production and presence of amniotic fluid. **Thus, assessing amniotic fluid levels is of utmost importance when evaluating any fetus with a urology diagnosis.**

IMPORTANT SONOGRAPHIC SIGNS AND GRADING

To put the severity of anomalies in proper context, the urologist must be familiar with pertinent grading systems and sonographic signs that may portend a urological anomaly. **Because urine is the primary constituent of amniotic fluid in the second half of pregnancy, decreased amniotic fluid index may be an important sign that urinary tract anomalies are present. Multiple studies suggest a near 100% mortality for patients with severe, untreated oligohydramnios in the second trimester**.[10, 11] Oligohydramnios is an independent predictor of survival and renal function in boys with lower urinary tract obstruction from posterior urethral valves (PUV).[12]

Specific sonographic findings in the kidneys, ureters and bladder guide the discussion that urologists have with expectant parents. Often the first sign of a urinary tract problem is the detection of antenatal hydronephrosis for which 3 different classification systems exist,[13] including the 1) anterior posterior diameter measurements of the renal pelvis,[14] 2) Society for Fetal Urology grading system[15] and 3) Urinary Tract Dilatation Classification system.[16] The Appendix shows the factors comprising these systems, and thresholds for the second and third trimesters of pregnancy.

Subjective terms such as mild, moderate and severe are often used to describe ANH but consistent application of 1 of the 3

ABBREVIATIONS: ANH (antenatal hypertension), APD (anterior posterior diameter), BE (bladder exstrophy), CE (cloacal exstrophy), LUTO (lower urinary tract obstruction), MCDK (multicystic dysplastic kidney), MMC (myelomeningocele), PBS (prune belly syndrome), PUV (posterior urethral valves), SFU (Society for Fetal Urology), UPJO (ureteropelvic junction obstruction), UTD (Urinary Tract Dilatation), VAS (vesicoamniotic shunt), VCUG (voiding cystourethrography), VUR (vesicoureteral reflux)

systems is preferred. APD measurements of the renal pelvis represent the simplest and perhaps most widely applied method for grading ANH. APD measurements are obtained from a transverse axial image of the renal pelvis at approximately the level of the renal hilum.[14] While the Appendix lists multiple measurements, the APD system can be simplified to the 3 values of 4 mm, 7 mm and 15 mm. **That is, APD >4 mm in the second trimester and 7 mm in third trimester are considered abnormal. APD measurements >15 mm at any time during gestation indicate severe ANH, and correlate with substantial risk for postnatal obstructive pathology and need for postnatal evaluation**.[17] The SFU and UTD systems add sophistication to the assessment by incorporating additional factors as shown in the Appendix. APD measurements can be used as a starting point and further classification can be derived from referencing either the SFU or UTD systems.

No defined system exists to guide the interpretation of prenatal ureteral and bladder size. Normally, the ureters are not visible during fetal ultrasound and thus, a ureteral diameter of <5 mm is reported to be physiological.[18] **Multiple reports suggest that first trimester bladder diameter should be 6 to 8 mm when measured in a longitudinal plane and that measurements >12 mm are abnormal.**[8, 19] In the second and third trimesters normal bladder size has not been defined but studies consider failure of the bladder to empty during a 40-minute fetal sonogram to be abnormal.[19] **Conversely, if the bladder is not seen on second trimester ultrasound, repeat bladder images should be obtained later in the study or a subsequent ultrasound should be done as non-visualization of the bladder can be a sign of severe bladder anomalies.**

PRENATAL UROLOGICAL ANOMALIES AND DIAGNOSES

The common potential diagnoses are reviewed with the goal of providing the key sonographic findings that help determine risk and an expectation of the postnatal natural history. **ANH is frequently seen on prenatal ultrasound and is associated with many other prenatal diagnoses.** Table 1 depicts the most common urology diagnoses in 609 patients from the Euroscan study, a European screening study of more than 700,000 patients.[20] Table 1 also indicates the key features of each diagnosis as well as the common postnatal management.

Hydronephrosis. Fetal ultrasound has high sensitivity for detecting urinary tract dilatation and is an ideal tool for identifying hydronephrosis. **A meta-analysis of 17 studies identified a 1.6% prevalence of ANH in 1678 fetuses from a total screened population of 104,572 infants.**[21] **These data correspond well with other studies, suggesting a 1% to 2% yearly incidence of ANH**.[16]

Table 2 shows the common causes of ANH. Once ANH is identified, the consulting urologist must determine which patients have substantial risk for true postnatal pathology. A positive correlation exists between increasing ANH grade and true postnatal pathology. **In the meta-analysis by Lee et al ANH defined as mild, moderate or severe using APD measurements conferred risk for diagnosing true urinary tract pathology in 12%, 45% and 88% of cases, respectively.**[21]

Transient hydronephrosis. Transient hydronephrosis, sometimes referred to as physiological hydronephrosis, represents a substantial proportion of patients with ANH. **Most cases of lower grades of ANH will resolve during the postnatal course without intervention or febrile urinary tract infection (UTI).** Data from the prospective SFU antenatal hypertension registry revealed that ANH resolved in 74% of patients with SFU grade I and 58% with SFU grade II.[22] Furthermore, fewer than 20% of patients with low grade ANH (SFU grade I/II) exhibited worsened hydronephrosis and fewer than 10% proceeded to surgical intervention. Additional prospective data on low grade ANH (SFU grade I/II) indicate that only 1% to 2% of patients will eventually require surgery and only 2% to 4% will experience a febrile UTI.[23] While it remains important to evaluate all newborns postnatally, the risk for postnatal pathology with lower grades of ANH appears to be low.

Ureteropelvic junction obstruction. Ureteropelvic junction obstruction is the most common etiology of ANH that will require surgical intervention. A narrowed, aperistaltic ureteral segment most commonly causes UPJO.[24] Mucosal folds, ureteral polyps and compression from lower pole crossing vessels are less common causes of UPJO. In some patients secondary UPJO may occur from tortuosity seen with a dilated ureter with or without vesicoureteral reflux. ANH caused by UPJO is asymptomatic in most newborns. As shown in figure 1, ultrasound findings that characterize UPJO include a dilated renal pelvis, dilated peripheral calyces, normal bladder and absence of ipsilateral ureteral dilation.[25]

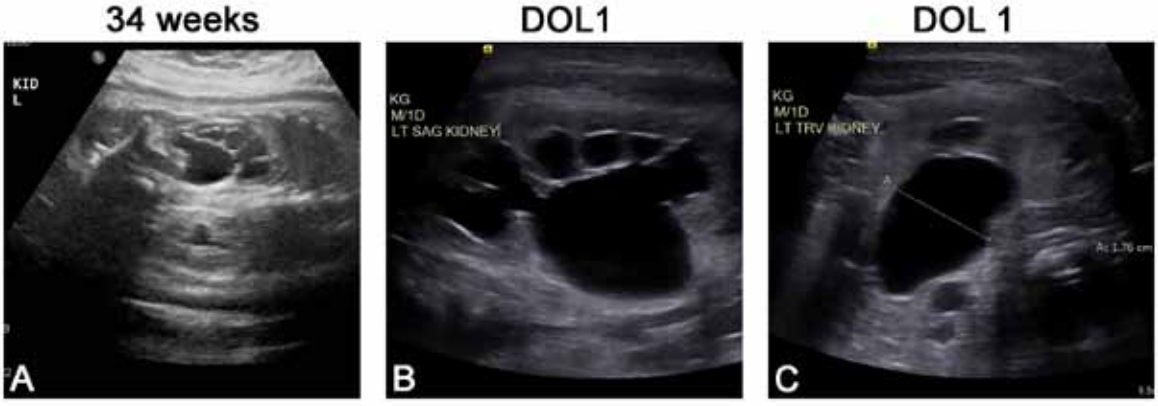

Figure 1. Prenatal and postnatal appearance of prenatally diagnosed ureteropelvic junction obstruction. *A*, fetal kidney at 34 weeks of gestation with dilated renal pelvis and peripheral calyceal dilation. *B*, postnatal ultrasound with large dilated pelvis and peripheral calyces without ipsilateral ureteral dilation. *C*, anterior posterior renal pelvis diameter.

Once ANH is identified, the urologist should counsel the expectant parents about the likelihood of postnatal surgery. While all patients with ANH should be followed postnatally, those with higher grades of ANH require closer monitoring. **Multiple series suggest that 20% to 30% of infants with ANH will ultimately undergo pyeloplasty for UPJO**.[24, 26] In 1 study neonates with APD >15 mm, calyceal dilatation and renal function >40% were randomized to immediate surgery or conservative management using ultrasound and diuretic renography.[27] At 1 year of follow-up only 19% of patients in the conservative group proceeded to surgery due to a decline in renal function. Not surprisingly, increasing grades of ANH (SFU grade III/IV) and renal APD (>20 mm) are associated with higher rates (50% to 55%) of surgical intervention.[28] **Parents should understand that while few infants undergo immediate postnatal surgery for UPJO, continued care is needed during the newborn period to ensure that signs of progressive obstruction do not develop.**

Finally, while the fetus with isolated unilateral hydronephrosis is often monitored by maternal fetal medicine specialists with serial ultrasounds, the benefit of this approach is unproved, and few fetuses suspected of UPJO require delivery at a tertiary care center if all other aspects of the pregnancy are reassuring.

Vesicoureteral reflux. VUR is another common cause of ANH that should be considered because of the risk of pyelonephritis in the newborn period. **While reports indicate that 1% of healthy newborns have VUR**,[25] **it will be seen on postnatal voiding cystourethrography in 8% to 40% of newborns diagnosed with ANH.**[29–32] **The AUA guidelines on the management of VUR conclude that the presence of VUR does not strongly correlate with severity of ANH irrespective of the grading system (SFU, UTD, APD) used to classify the hydronephrosis**.[32] That is, VUR is equally likely to be present in the neonate with less severe ANH as it is in the neonate with more severe ANH. While the AUA guidelines recommend VCUG in children with higher grades of VUR (SFU grade III/IV), the decision to perform it will be made postnatally based on family history of VUR, comorbid conditions, additional urinary tract findings, risk for urinary tract infection and circumcision status.

Multicystic dysplastic kidney. **MCDK is a form of renal dysplasia and is the most common cause of cystic kidney disease in children.**[33] It is commonly diagnosed prenatally and must be considered given the fact that the neonate will be born with a solitary functioning kidney.[34] In some cases MCDK can be mistaken for ANH and thus, it is included in tables 1 and 2. **Postnatal findings that can distinguish MCDK are an ultrasound showing multiple cystic lesions of variable size that do not communicate (as opposed to hydronephrosis which typically demonstrates communication), a lack of parenchyma between cysts and a nuclear medicine renogram demonstrating a lack of cortical function.**

Two predominant theories exist to explain the development of MCDK. One theory suggests that MCDK forms due to severe obstruction, such as UPJO or ureterovesical junction obstruction, in the urinary tract that occurs early during gestation.[35] A second theory proposes that abnormal interaction between the ureteric bud and the metanephric blastema leads to cystic dysplasia and abnormal development.[36] Figure 2 shows the characteristic appearance of MCDK. **Anomalies, including VUR (20%) and UPJO (5%), can be present in the contralateral kidney in approximately a third of patients.**[37] While historically VCUG was routinely performed in children with MCDK, recent data question this practice because the VUR identified on routine VCUG is often low grade and has a high likelihood of spontaneous resolution.[38] **The rate of involution of MCDK on ultrasound is reported to be 60% within 10 years.**[39]

Megaureter. The fetus may present with significant ureteral dilatation with or without dilation of the renal pelvis. The presence of unilateral ureteral dilatation alone without signs of lower urinary tract obstruction suggests a diagnosis of primary megaureter. **A ureteral diameter >7 mm defines a megaureter**.[18] The typical etiology of primary megaureter is a ureterovesical junction obstruction caused by disordered development of the distal ureter and the ureterovesical junction similar to UPJO. Postnatally, the combination of VCUG and postnatal renal scan broadly classifies megaureters as obstructed, refluxing, non-refluxing/non-obstructed and refluxing/obstructed. In general, **postnatal surgery for isolated megaureter is reported to be low.** Data show that primary megaureter will resolve spontaneously without surgical intervention in 70% of cases.[40] Factors that predict the decision for surgery in children with primary megaureter include increasing ureteral diameter, higher grades of hydronephrosis (SFU grade III/IV) and decreased

Figure 2. Prenatal and postnatal appearance of right multicystic dysplastic kidney. *A*, right kidney at 26 weeks of gestation (dashed oval) with presence of multiple non-communicating cysts and minimal parenchyma between cysts. Left kidney demonstrates hydronephrosis. *B*, right kidney on ultrasound at DOL0. *C*, diuretic nuclear medicine renogram at age 5 years shows no right renal function and slow drainage of left kidney.

Table 1. Most common congenital urological anomalies, features and management[20]

Anomaly	% Total	% Detected Prenatally	Key Prenatal Features	Common Postnatal Management Steps
Hydronephrosis	51	84	Most common prenatal finding, does not warrant early delivery if isolated unilateral finding	No immediate postnatal management, ultrasound minimum 48 hrs after delivery, prophylactic antibiotics use and VCUG varies
Multicystic dysplastic kidney	17	97	Multiple non-communicating renal cysts, minimal visible parenchyma, often confused with hydronephrosis	No immediate postnatal management, ultrasound minimum 48 hrs after delivery, referral to pediatric urology in first month of life
Unilateral renal agenesis	10	62	Single hypertrophied kidney, flattened or ovoid adrenal gland on ipsilateral side	No immediate postnatal management, ultrasound minimum 48 hrs after delivery
Duplicate kidney	6	95	Hydronephrosis with possible ureterocele in the bladder, more common in females, longer kidney on the side of duplication, ureteral dilation possible	No immediate postnatal management unless hydronephrosis is severe, ultrasound minimum 48 hrs after delivery, prophylactic antibiotics use and VCUG vary, referral to pediatric urology in first month of life
Posterior urethral valves	4	70	Prenatal intervention possible in select cases at experienced centers, oligohydramnios possible and may impact survival and lung function, male gestation with bladder wall thickening and keyhole sign, unilateral or bilateral hydronephrosis	Immediate postnatal management needed, ultrasound first 24 hrs after delivery, urology consultation after delivery for catheter placement if not voiding, VCUG if suspicion for diagnosis is high, nephrology consult and intensive care may be needed if oligohydramnios present
Bladder exstrophy	3	53	Non-visualization of the bladder, low set umbilical cord insertion, soft tissue mass on lower abdomen	Immediate postnatal management needed, urology consultation after delivery, topical care and protection of the open bladder plate with petroleum jelly and plastic wrap, referral to experienced center for discussion of closure
Myelomeningocele			Prenatal intervention possible at experienced centers, lemon sign, banana sign	Immediate postnatal management suggested, ultrasound minimum 48 hrs after delivery, coordination of back closure with neurosurgery, intensive care often needed, begin clean intermittent catheterization after delivery given risk for poor bladder emptying following closure, multidisciplinary newborn and lifelong follow-up suggested with repeat ultrasound and baseline urodynamic testing at age 3 mos

Myelomeningocele not included in Wiesel et al.[20]

Table 2. Common causes of antenatal hydronephrosis[13]

% Diagnosis
Transient hydronephrosis 41-88 Ureteropelvic junction obstruction 10-30 Ureterovesical junction obstruction/megaureter 5-10 Ureterocele/duplex collecting system 5-7 Multicystic dysplastic kidney 4-6 Lower urinary tract obstruction (posterior urethral valves and urethral atresia) 1-2

renal function.

Renal duplication. Duplication of the renal collecting system represents one of the most common anomalies seen in the urinary tract, and prenatal diagnosis is possible. **Complete duplication is believed to occur in 1% of the population while incomplete duplication appears more frequently in 1 out of 500 people.**[41] Altered signaling during the first few weeks of development leads to the induction of more than 1 ureteric bud from distal nephric duct which causes duplication upon contact with the metanephric mesenchyme. Based on the Weigert-Meyer law, the upper pole ectopic ureter arises from the nephric duct superior to the lower pole ureter but when the distal nephric duct is absorbed into the developing bladder, a 180-degree rotation of the ureteric buds occurs and the upper pole ureter migrates to a caudal, ectopic position in the bladder.

The common associations seen in patients with complete duplication include lower pole VUR and upper pole obstruction due to the ectopic ureter with or without a ureterocele.[42] Fetal ultrasound findings that suggest a duplication include longer renal length on the side of duplication, a dilated upper pole ureter, presence of a ureterocele and an upper pole cyst.[43] The simple finding of a duplicated collecting system on prenatal ultrasound does not warrant specific changes in care or postnatal monitoring beyond repeat ultrasound. However, when hydronephrosis, ureteral dilation and/or a ureterocele is present, further evaluation will be required postnatally. The family will need to understand the importance of evaluating the newborn for VUR and upper pole obstruction, particularly when a ureterocele is present. Finally, the family must understand that in some cases neonatal surgery to address an obstructed upper pole may be required.

Renal agenesis. Whether bilateral or unilateral, renal agenesis occurs when the ureteric bud fails to interact properly with the metanephric blastema.[44] Bilateral renal agenesis occurs in 1 to 3 of every 10,000 live births and is incompatible with life.[45] **Unilateral renal agenesis more commonly occurs in 1 of every 1000 live births. Additional urological findings are noted in nearly 50% of patients with unilateral agenesis including VUR (28%) and UPJO (7%).**[46] Internal genital duct abnormalities may also be identified with males showing ipsilateral abnormalities of the vas deferens. Females may have duplication anomalies of the uterus or vagina, vaginal agenesis or fallopian tube anomalies.[47] Isolated unilateral renal agenesis should not alter the course of pregnancy or necessitate changes in delivery planning.

LOWER URINARY TRACT OBSTRUCTION

The suspicion of fetal lower urinary tract obstruction should raise a greater level of concern and requires closer monitoring during gestation than almost any other prenatal diagnosis. These patients are at high risk for intrauterine fetal demise and those who survive will likely need subspecialty care including serial fetal ultrasounds and postnatal care at a tertiary medical center. Fetal intervention to relieve obstruction may also be considered. **The ultrasound findings most suggestive of fetal LUTO include male gender, moderate to severe hydronephrosis (unilateral or bilateral), renal cortical cysts, an enlarged thickened bladder (megacystis), a dilated posterior urethra (keyhole sign) and oligohydramnios or anhydramnios.**[48] Figure 3 shows the characteristic fetal ultrasound images of postnatally confirmed LUTO.

Certain sonographic signs are more important than others in helping to determine risk for fetal demise and risk for renal impairment in patients with LUTO. **A systematic review of 13 studies and 215 fetuses with postnatally confirmed LUTO revealed that the best predictors of impaired renal function were abnormal renal cortical appearance (echogenic renal parenchyma echogenicity or cortical cysts) and the presence of oligohydramnios.**[49] Likewise, the presence of oligohydramnios before 26 weeks of gestation is a poor prognostic sign for survival and postnatal renal function.[50]

The 3 diagnoses associated with most cases of LUTO are posterior urethral valves, urethral atresia and prune belly syndrome (PBS) (also known as Eagle-Barrett syndrome). While ultrasound provides excellent sensitivity for identifying signs of LUTO, significant overlap may occur in the clinical presentation of each entity on ultrasound. Thus, distinguishing among these diagnoses can be a challenge. In 1 study the sensitivity of ultrasound for detecting PUV was 94% while the diagnostic specificity was only 34%.[51] Fetal intervention is possible for patients with suspected LUTO.

Posterior urethral valves. **Posterior urethral valves represent the most common form of LUTO and occur in 1 of every 8000 live male births.** LUTO in boys with PUV is a consequence of a congenital obstructing membrane in the posterior urethra causing complete or partial bladder outlet obstruction.[52] Progressive obstruction during gestation leads to megacystis, bladder wall fibrosis, hydronephrosis, renal dysplasia and possibly pulmonary insufficiency. **End stage renal disease develops in 30% of boys with PUV, occurring primarily in the first 3 decades of life.**[53] Multiple factors may predict the need for

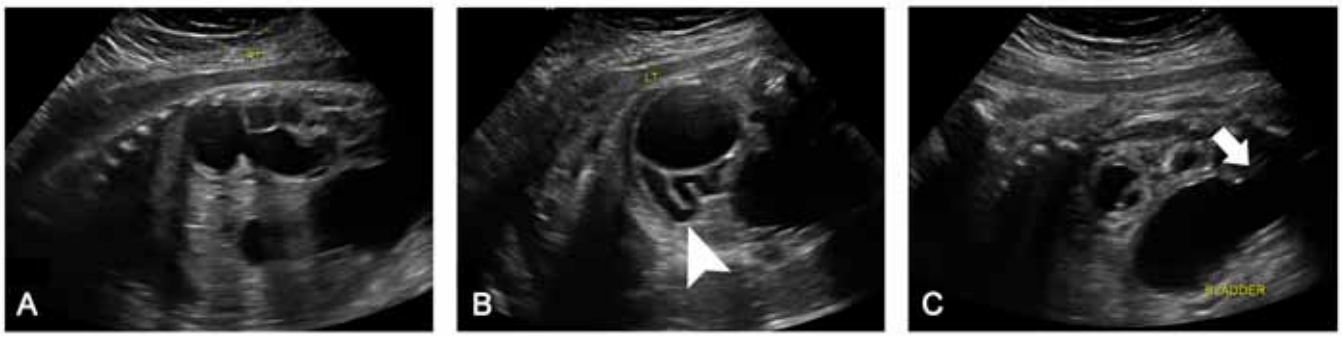

Figure 3. Sonographic appearance of kidneys and bladder in male fetus at 33 weeks of gestation with postnatal diagnosis of posterior urethral valves. *A*, dilated renal pelvis and calyces of right kidney. *B*, large left renal pelvis with dilated and tortuous ureter (arrowhead). *C*, bladder with megacystis and keyhole sign (arrow) in which dilated posterior urethra is seen.

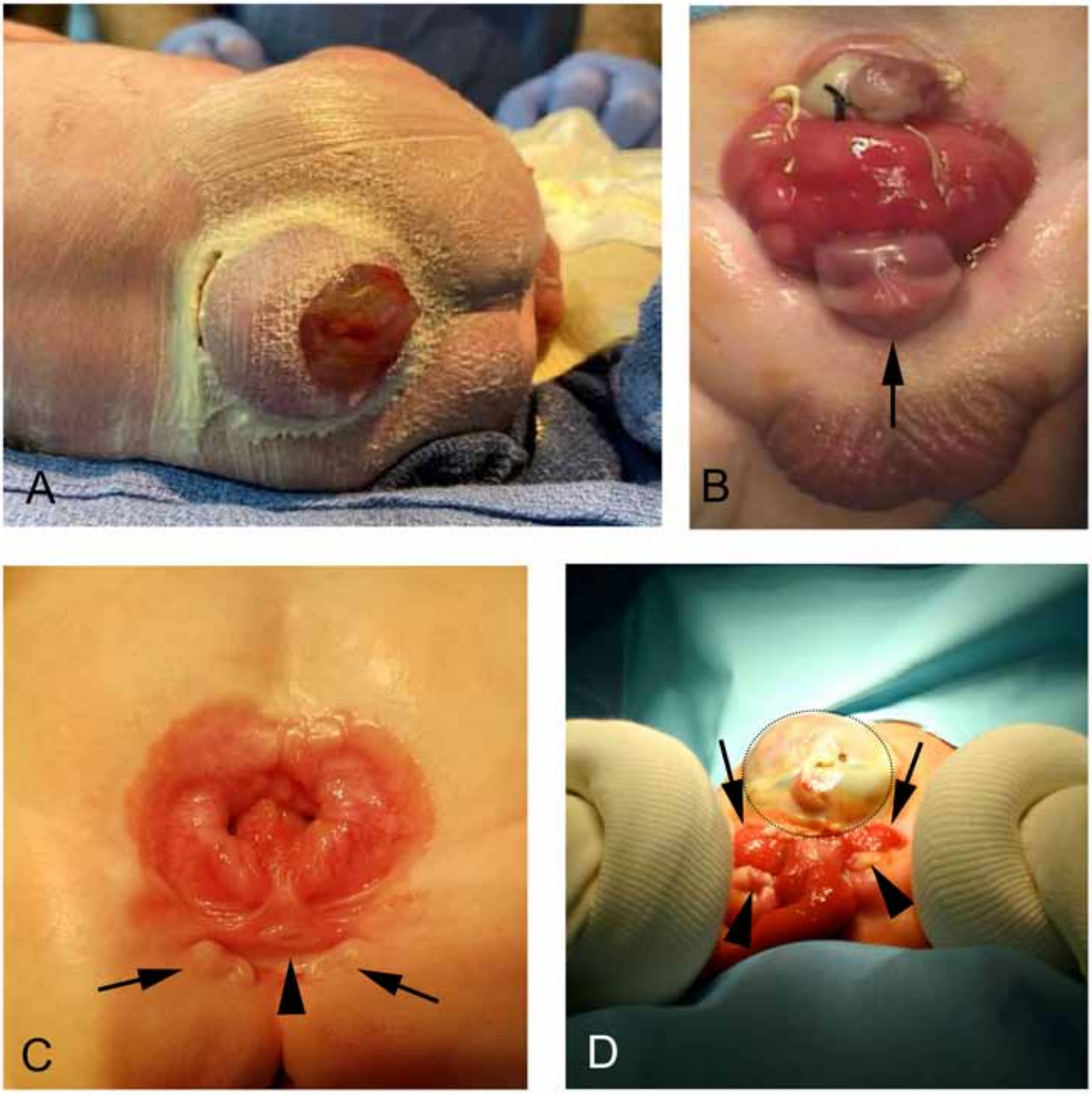

Figure 4. Appearances of myelomeningocele, bladder exstrophy and cloacal exstrophy. *A*, MMC with spinal contents herniating through open defect in lower back of male newborn. *B*, classic bladder exstrophy in male. Note open bladder plate above penis (arrow). *C*, classic bladder exstrophy with open bladder plate, widely separated clitoral bodies (arrows) and vagina in center (arrowhead). *D*, cloacal exstrophy in female. Bladder plate is separated into halves (arrows) and intestine is present between each half with characteristic "elephant trunk" appearance. Note large omphalocele (dashed oval) and divergent clitoral bodies on either side of intestine (arrowheads).

dialysis including vesicoureteral reflux, urinary tract infection, need for clean intermittent catheterization and nadir creatinine in the first year of life.[54] **Yet data from a recent large multicenter study indicate that risk for renal replacement in the first 10 years of life is best predicted by serum nadir creatinine in the first year.[55] Of infants with serum nadir creatinine >1.0 mg/dL progressed to renal replacement was required by age 10 years in 100% compared to none with nadir creatinine <0.4 mg/dL.**

Urethral atresia. Severe urethral hypoplasia during development can result in complete obstruction known as urethral atresia. Its exact incidence remains difficult to assess due to the near universal lethality of the diagnosis. Almost no fetus with urethral atresia can survive without means to decompress the bladder either through a fetal procedure or via a patent urachus.[56]

Prune belly syndrome. PBS is a triad of urological findings

characterized by deficiency or absence of abdominal wall musculature, urinary tract dilatation of varying severity and intra-abdominal testicles. An estimated 3.8 per 100,000 live male births are affected by PBS.[57] The LUTO in patients with PBS is classically believed to occur from hypoplasia and redundancy of the prostatic urethra. Although rare, urethral atresia has been reported in association with PBS.[58] Regardless of the cause of LUTO, patients with PBS are at high risk for prematurity, fetal death, perinatal mortality and renal failure.[59]

Diagnoses that mimic LUTO. Several rare entities may mimic the traditional causes of LUTO and should be considered when megacystis is present but signs of LUTO are absent. These rarer mimics include megacystis microcolon intestinal hypoperistalsis syndrome, isolated congenital megacystis and megacystis megaureter association. Megacystis microcolon intestinal hypoperistalsis syndrome predominately affects the female fetus (3:1) and is defined by dilated small bowel, microcolon with malrotation and non-obstructive megacystis with or without hydronephrosis.[60] In addition to female gender, the syndrome is suggested by elevated digestive enzymes on amniocentesis and elevated calcium levels on vesicocentesis.[61] It is often lethal with few infants surviving beyond the first few years of life.

Isolated congenital megacystis is believed to be a milder variant of megacystis microcolon intestinal hypoperistalsis syndrome or perhaps a form of visceral myopathy.[62] Megacystis megaureter association is defined by a large, thin-walled bladder with hydronephrosis. Large volume VUR with repeated cycling of urine between the bladder and upper tracts creates a "yo-yo" reflux, leading to progressive bladder and ureteral distension. On prenatal ultrasound a thin-walled bladder, hydroureteronephrosis and normal amniotic fluid volumes characterize this condition.[63]

SEVERE BLADDER ANOMALIES

Prenatal development of severe bladder anomalies like bladder exstrophy and cloacal exstrophy is possible (fig. 4). In the United States BE occurs in approximately 2 per 100,000 live births while cloacal exstrophy occurs in 1 in 200,000 live births.[64] BE results from failure of the lower abdominal wall to close properly during fetal development. The defect leaves the skin, rectus muscles, genitalia and pubic bones widely separated in the midline. The bladder lumen is splayed open as an exposed, flat plate on the lower abdomen. CE, an even rarer and more severe variant, has features similar to bladder exstrophy except the bladder plate is separated into 2 halves with herniation of the intestines between the halves. A large omphalocele is also typically present.

Select ultrasound criteria can aid in the diagnosis of BE and CE. **Ultrasound findings suggestive of BE are non-visualization of the bladder in a fetus with normal kidneys and amniotic fluid index, a midline infraumbilical soft tissue mass and low set umbilical cord insertion.**[65] **Criteria that support the diagnosis of CE are non-visualization of the bladder in a fetus with normal kidneys and amniotic fluid index, a large midline infraumbilical anterior wall defect or cystic anterior wall structure, omphalocele and myelomeningocele.**[66] Studies suggest that 25% to 50% of BE and CE cases are diagnosed prenatally.[20,67] For suspected BE or CE, fetal magnetic resonance imaging may be used to further confirm the diagnosis.[68] Identifying these anomalies early permits prenatal consultation with a multidisciplinary team, proper delivery planning at a tertiary center and discussion of pregnancy termination.

SPINA BIFIDA

Newborn survival of spina bifida has greatly improved over time due to refinements in neurosurgical care and the ability to perform ventriculoperitoneal shunting. While survival at age 1 year in 1950 was reported to be only 20%, between 2001 and 2012 modern care has improved survival at age 5 years to approximately 90% in Europe and North America.[68,69]

While not specifically a urology diagnosis, the urologist must be familiar with prenatal diagnosis of spina bifida, particularly myelomeningocele included in a heterogeneous group of open neural tube defects. Dorsal closure of the developing neural tube occurs at 4 weeks of gestation. Failure of the neural tube to close properly leaves a soft tissue and bony defect which, combined with herniation of the spinal cord and meninges through the open defect, defines MMC (fig. 4). The urologist must prepare the family for the possibility of neurogenic bladder dysfunction after birth and the need for lifelong urological care.

Second trimester ultrasound can identify open neural tube defects like MMC, although sonographic findings in the fetal brain are often the first clue to the diagnosis. **Studies show that the "lemon" sign (indentation or scalloping of the frontal bones) and the "banana" sign (elongation and downward displacement of the cerebellum) are frequently present in patients with open neural tube defects like MMC, and these findings should prompt detailed assessment of the fetal spine.**[70] Additionally, the field of fetal surgery has progressed such that fetal MMC repair is now offered across the United States and abroad. When counseling the parents of a fetus with prenatally diagnosed MMC, the urologist must mention the need for early postnatal urological evaluation with ultrasound and urodynamics, the low likelihood of toilet training and volitional voiding, and the high likelihood of medical and surgical management of neurogenic bladder over time.

IMPLICATIONS FOR DELIVERY AND FETAL INTERVENTION

Most prenatal urology diagnoses are managed conservatively with serial fetal ultrasounds which are repeated in the postnatal period. Few diagnoses ultimately require delivery at a tertiary medical center. **A postnatal renal/bladder ultrasound should be obtained a minimum of 48 hours after birth to permit resolution of neonatal dehydration which may underestimate the degree of hydronephrosis present**.[71] Fetuses with LUTO, severe bladder anomalies and MMC warrant delivery at a tertiary facility with access to a neonatal intensive care unit, pediatric nephrologists, urologists and neurosurgeons. Some fetuses with LUTO and MMC may also be candidates for fetal intervention.

LUTO intervention. Fetal intervention for LUTO originated in preclinical animal studies in the early 1980s.[72] Decompression of the fetal bladder to improve amniotic fluid levels remains the goal of fetal intervention for LUTO. As gestation progresses, fetal urine becomes increasingly hypotonic as electrolytes are reabsorbed by the fetal kidney.[73] In the 1990s percutaneous fetal urine sampling (vesicocentesis) was used to assess the hypotonicity of fetal urine in patients with LUTO

with the hope of predicting renal outcome.[74] Serial vesicocentesis allows cases to be categorized as favorable and unfavorable based on fetal renal function. Fetal urinary biochemical values considered to be favorable for renal function are sodium <100 mmol/L, calcium <8 mg/dL, chloride <90 mmol/L, osmolality <200 mmol/L, total protein <20 mg/dL and beta-2-microglobulin <6 mg/dL.[75]

With fetal urine electrolyte data available, fetal intervention can then be considered. The 2 primary methods for decompressing the bladder are vesicoamniotic shunts and fetal cystoscopy, although VAS placement remains the most thoroughly studied. VAS placement is achieved with an ultrasound guided percutaneous procedure with the patient under maternal intravenous sedation and/or local anesthesia. After identifying the fetal bladder, a double pigtailed shunt catheter is placed into the bladder with the opposite end residing in the amniotic space.[76] Fetal cystoscopy is also a percutaneous ultrasound guided procedure using similar maternal and fetal anesthesia. Small 1.0 to 1.3 mm fetoscopes are placed via a sheath and cystoscopy is performed allowing the valves to be incised.[77]

Data regarding survival and renal function with fetal intervention come primarily from VAS studies. Individual series report newborn survival rates following VAS placement of 40% to 90%.[75,78] The only randomized controlled trial comparing VAS placement with conservative management revealed a modest survival benefit after shunt placement, and the majority of surviving patients had poor renal function despite shunt placmenet.[79] Data from a meta-analysis of 9 studies confirmed that even in children who survive following VAS placement, renal function is no different compared to conservative management.[80] **Thus, parents of the fetus with LUTO who elect fetal intervention with a VAS must be prepared for the possibility of persistent poor renal function.**

Fetal repair of MMC is now offered across the United States due to the landmark randomized controlled trial MOMS (Management of Myelomeningocele Study) which compared prenatal and postnatal repair. Retrospective and prospective data showed that prenatal repair of MMC significantly reduced the need for ventriculoperitoneal shunt insertion. With these positive data, the National Institutes of Health funded the MOMS trial beginning in 2009. In that trial prenatal repair led to a 42% reduction in ventriculoperitoneal shunt placement, and resulted in improvement in mental development and motor function scores compared to postnatal closure.[81]

A more germane question to urologists is the impact of prenatal repair on bladder function in these patients. To date, almost all studies show that prenatal repair does not improve bladder function. Follow-up data from the MOMs trial indicate that some improvement in the ability to toilet train may exist following prenatal closure but rates of lower urinary tract reconstruction and urodynamic data to date have not shown prenatal repair to be beneficial.[82]

CONCLUSION

Most fetal patients present to the urologist as referrals from a maternal fetal medicine specialist with a diagnosis in mind. The role of the urologist is to provide the family with a reasonable assessment of risk. Furthermore, the urologist must be able to identify the most worrisome diagnoses including lower urinary tract obstruction, spina bifida and bladder exstrophy.

DID YOU KNOW?

- Of all pregnancies 2% to 3% are affected by a prenatal urology diagnosis.
- Antenatal hydronephrosis represents 40% to 50% of all prenatal diagnoses and most cases of low grade hydronephrosis will resolve during the first 2 to 3 years of life.
- Few urology diagnoses will require early delivery or delivery at a tertiary care center but diagnoses that should raise significant concern include lower urinary tract obstruction, spina bifida and severe bladder anomalies such as bladder exstrophy and cloacal exstrophy.
- Oligohydramnios is the greatest predictor of survival of fetuses with suspected lower urinary tract obstruction.
- Fetal intervention is possible at experienced centers when lower urinary tract obstruction or spina bifida is identified.

Appendix. Antenatal hydronephrosis grading systems

System Characteristics	Thresholds/Grading	
	Second Trimester (mm)	Third Trimester (mm)
Renal pelvis APD: measurement of fetal renal pelvis in transverse plane[14]	Mild 4-7, moderate 7-10, severe >10	Mild 7-9, moderate 9-15, severe >15
SFU system: fullness of renal pelvis, major and minor calyceal dilation, thickness of parenchyma[15]	No trimester specific criteria; SFU grades: I–minor splitting of the renal pelvis, II–filling of the renal pelvis, III–grade II plus major and minor calyces, IV–grade III plus thinning of the parenchyma	
UTD classification:* APD, parenchymal thickness, calyceal dilatation, parenchymal appearance, ureteral abnormalities, bladder abnormalities[16]	UTD A1: APD 4-7 mm with dilation of central renal pelvis only UTD A2-A3: APD >7 mm + any other characteristic	UTD A1: APD 7-10 mm with dilation of central renal pelvis only UTD A2-A3: APD >10 mm + any other characteristic

*UTD A1 is low risk and UTD A2-3 is intermediate risk.

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Study Questions Volume 39 Lesson 15

1. A 23-year-old woman is seen at 25 weeks of gestation concerned about bladder exstrophy. She has a singleton fetus with normal amniotic fluid levels. The ultrasound finding most concerning for bladder exstrophy is
   a. keyhole sign
   b. ambiguous genitalia
   c. non-visualized bladder
   d. bilateral hydronephrosis

2. The ultrasound parameter that is most worrisome for overall survival in a male fetus suspected of having lower urinary tract obstruction based on second trimester screening ultrasound is
   a. kidney size
   b. hydronephrosis grade
   c. amniotic fluid level
   d. bladder wall thickness

3. A 28-year-old woman has an ultrasound performed at 27 weeks of gestation which shows a singleton male fetus with bilateral hydronephrosis, renal cysts, dilated ureters and a thick-walled bladder. Amniotic fluid levels are normal. The parents want to know the risk for kidney failure over the course of the child's life. The postnatal parameter that has the capacity to predict the need for dialysis is
   a. nadir creatinine in the first year of life
   b. appearance of the renal parenchyma
   c. recurrent urinary tract infection
   d. presence of high grade vesicoureteral reflux

4. A multicystic dysplastic kidney is characterized by
   a. cystic renal parenchyma
   b. multiple non-communicating cysts
   c. dilated renal pelvis
   d. peripheral calyceal dilatation

5. The most common anomaly seen in the contralateral kidney of a patient with a multicystic dysplastic kidney is
   a. renal duplication
   b. ureteropelvic junction obstruction
   c. vesicoureteral reflux
   d. ureterocele

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