Prenatal Consultations

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Section summary:

This chapter is designed to serve as a guide for individuals involved in the prenatal care and counseling of families affected by genitourinary conditions.

1. Introduction:

Given the broad scope of conditions discussed herein, and particularly for more in depth explanations of postnatal management considerations, this chapter should be used in conjunction with those chapters that are dedicated to specific diagnoses. Additionally, due to the fact that complex prenatal care typically involves multiple subspecialty providers, some of the management strategies described here may not be directed by the urologist at the majority of centers. In this case, the details of care are provided primarily for context.

2. Prenatal Evaluation and Care

Prenatal care may be guided by a range of provider types, including family physicians, certified midwifes, nurse-midwifes and obstetricians. Additionally, a maternal fetal medicine physician may become involved in the case that higher risk conditions are identified in either the mother or fetus. Subspecialty providers, including pediatric urologists, may provide consultation at the primary or maternal-fetal medicine provider’s discretion when there is concern for fetal risks or problems related to the urinary tract or genitalia.

The content and timing of prenatal care is not standardized and instead dictated by the needs and risk status of the mother and fetus.[1] Below are commonly employed prenatal testing modalities that may identify or predispose to urologic abnormalities in the fetus.

2.1 Imaging

2.1.1 Fetal Ultrasound

Ultrasonography is the most commonly used fetal imaging tool with the average number of ultrasounds obtained per pregnancy estimated to be 2.7 (2.1 for low-risk and 4.2 for high-risk).[2] Depending on the gestational age at which fetal ultrasound is performed, information regarding the anatomy and health of the kidneys, ureters, bladder and reproductive structures may be garnered. The overall estimated sensitivity of ultrasound in detecting urinary tract anomalies prenatally is approximately 90% [3,4] and urologic anomalies account for 20-30% of all prenatally detected congenital abnormalities. [5] One third of patients with identified abnormalities[6] of the urinary tract will be found to have an anomaly in another organ systems and/or will be identified to have an associated syndrome.[3]

First trimester ultrasound (prior to 14 weeks gestation) is typically performed to confirm the presence of an intrauterine pregnancy and to estimate gestational age. Assessment for certain fetal anomalies including for signs of fetal aneuploidy may be performed however, evaluation of the urogenital tract in the first trimester is generally limited by the small size of the fetus and ongoing fetal development.

Ultrasound screening for structural fetal anomalies is typically performed in the second trimester, between 18 and 22 weeks of gestation. The following features should be evaluated:

Table 1

Urinary Tract	**Kidneys:** location, number, volume and echogenicity, presence of cysts, pelvocaliceal and/or ureteral dilation. Measurement of the renal pelvis (when visible) should be performed in the anterior-posterior direction in the transverse view **Bladder:** presence (cycles with an average frequency of 25-30 min), volume and wall thickness
External Genitalia	**Female:** Presence of labia, clitoris **Male:** Presence of scrotum, testicles, penis
Internal Genitalia	**Female:** Uterus (after 19 weeks)[7]
Amniotic Fluid	Volume analysis and echogenicity. Fetal urine becomes major contributor to amniotic fluid by approximately 20 weeks.[8,9]

Adapted from Bunduki,V and Zugaib, M. (2018). Atlas of Fetal Ultrasound: Normal Imaging and Malformations. Springer International Publishing.

2.1.2 Fetal Magnetic Resonance Imaging

Fetal magnetic resonance imaging (MRI) may be utilized as a complement to ultrasound imaging in order to further delineate fetal anatomy. It is favored over CT due to the lack of associated radiation and may be of particular benefit where such factors as maternal habitus, fetal position, fetal shadow bone artifact or decreased amniotic fluid levels limit the quality of ultrasound images. [10] Prenatal MRI is not standard practice due to its high cost.

2.2 Laboratory Testing

2.2.1 Diabetes mellitus screening

All pregnant women should be screened for gestational diabetes mellitus (GDM) between 24-48 weeks GA.[1] Poorly controlled maternal diabetes is associated with an elevated risk of neural tube defects.[11] Studies examining the relationship between maternal diabetes and sacral agenesis have demonstrated pregestational diabetes to be a known risk factor while some data suggests a similar association between gestational diabetes and sacral agenesis.[12] Studies have also noted an association between maternal diabetes and renal agenesis/dysgenesis. [13]

2.2.2 Maternal serum alpha-fetoprotein

Maternal serum alpha-fetoprotein is used in conjunction with fetal anatomy survey to assess for neural tube defects, typically between 16-18 weeks gestation. A value greater or equal to 2.0 or 2.5 multiples of median (MoM) is considered abnormal.

2.2.3 Genetic evaluation

ACOG guidelines recommend that all pregnant mothers should be offered assessment for aneuploidy regardless of maternal age or risk of chromosomal abnormalities.[14] Prenatal genetic screening assesses whether a fetus is at increased risk of being affected by a genetic disorder while testing confirms whether a specific genetic abnormality is present in the fetus.

Prenatal genetic screening may consist of serum labs (e.g. serum free Beta-hCG and PAPP-A) with or without nuchal translucency (NT) ultrasound or cell-free DNA (cfDNA). In the event that screening is positive, patients should be offered comprehensive ultrasound evaluation as well as genetic testing in order to confirm the screening results. [14]

Prenatal genetic testing is most commonly performed with fetal cells obtained by amniocentesis or chorionic villus sampling (CVS) using karyotype analysis and can detect all aneuploidies including trisomies and sex chromosome aneuploidies. Mosaicism in the fetus may not be detected if the mosaicism is not present in the fetal cell-type obtained for testing. [15]

3. Urinary Tract Dilation

Advances in obstetric ultrasound techniques and widespread adoption of prenatal ultrasound screening have allowed for improvements in early detection of urinary tract abnormalities, the most

common of which is urinary tract dilation. Urinary tract dilation is detected in 1-4.5% [16,17] of pregnancies, most often during the second trimester at the time of routine ultrasound examination.

Prenatal hydronephrosis may be associated with aneuploidy, particularly where co-occurring anomalies are diagnosed. The most commonly described association is between hydronephrosis and Down syndrome although isolated pyelectasis predicts concurrent Down syndrome with a likelihood ratio of only 1.5-2.4. [18,19] Thus, the majority of fetuses with isolated hydronephrosis will not have associated genetic abnormalities. Generally, karyotype should be considered on a case by case basis and particularly in the setting of associated extrarenal anomalies or when additional risk factors are present (e.g. advanced maternal age or positive lab serum screening).

3.1 Classification and clinical significance of antenatal urinary tract dilation

Prenatally diagnosed urinary tract dilation represents a finding and not a specific diagnosis. The large majority of antenatal hydronephrosis is due to physiologic hydronephrosis,[20] which does not require treatment. However, as fetal urinary tract dilation has the potential to be associated with illness and impairment of both renal and pulmonary function, the goal of management is to identify those individuals who may have adverse outcomes while limiting testing and anxiety in those where urinary tract dilation is likely due to a benign cause.

Classification systems allow practitioners to grade hydronephrosis in order to better categorize patient risk and outcomes which can help to inform both patient management and counseling. Widely employed classification systems include: 1) anterior-posterior renal pelvis diameter (APRPD), 2) Society for Fetal Urology (SFU) ultrasound grading system, and 3) Urinary tract Dilation (UTD).

3.1.1 Anterior-Posterior Renal Pelvis Diameter (APRPD)

APRPD is measured by ultrasonography in the mid-transverse view. APRPD is favored by the majority of maternal-fetal medicine physicians, in part due to its objective nature.[21] APRPD grading relies on a single measurement and does not include characteristics such as parenchymal appearance (e.g. thinning and echogenicity), associated ureteral or bladder abnormalities. Measurements are operator-dependent and may be influenced by hydration status of the mother [22,23] as well as fetal position.

The limits of what is considered] normal for APRPD has been demonstrated to increase through pregnancy.[24,25] In the 2nd trimester, APRPD greater or equal to 4 mm is the most common threshold for diagnosing urinary tract dilation while a diameter of greater or equal to 7 mm is typically accepted in the 3 rd trimester.[20] The degree of APRPD abnormality has been associated with the risk of postnatal surgery[26] as well as type of pathology.[27]

Table 2

	Mild	Moderate	Severe
2nd trimester (16-27 wks)	4-7 mm	7-10 mm	> 10 mm
3rd Trimester (28-32 wks)	7-8 mm	9-15 mm	> 15 mm
Any Pathology	» 12%	» 45%	» 90%
UPJ Obstruction	» 5%	»15%	» 55%
VUR	» 4%	» 15%	» 10%
PUV	» <0.5%	» 1%	» 5%
Ureteral obstruction	» 1%	» 10%	» 5%
Other	» 1%	» <5%	» 15%

Adapted from Lee RS, Centron MC Kinnamon DD et al. Antenatal hydronephrosis as a predictor of postnatal outcome: A meta-analysis. Pediatrics. 2006: 118(2): 586-93.

3.1.2 Society for Fetal Urology (SFU) Ultrasound Grading System

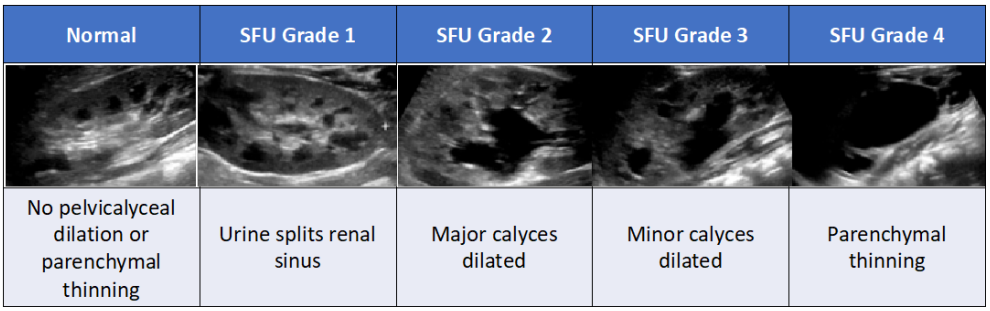

Figure 1: Adapted from Fernbach SK, Maizels M, Conway JJ. Ultrasound grading of hydronephrosis: introduction to the system used by the Society for Fetal Urology. Pediatr Radiol. 1993; 23(6): 478-80.

See Reference 28.

The SFU system is a 5-class system that was developed in 1993 and is used by the majority of pediatric urologists. [29,30] It incorporates three components: 1) subjective evaluation of the degree of dilation of the renal pelvis, 2) presence and/or absence of central (major) and peripheral (minor) calyceal dilation and 3) parenchymal thickness. There has been significant inter-rater and intra-rater variability noted with the SFU system, [31] particularly for SFU grades II/III.[32] SFU grade III/IV has been demonstrated to predict risk of urinary tract infection as well as need for postnatal surgery.[33]

3.1.3 Urinary Tract Dilation (UTD) Classification System

See Reference 34.

The UTD system was created in 2014 with the input of members representing eight medical societies. It includes both antenatal and postnatal grading systems, and provides separate criteria for each. In the case of antenatal grading, there are two categories. Grading is based on several criteria: 1) anterior-posterior renal pelvic diameter, 2) calyceal dilation (presence or absence), 3) renal parenchymal thickness (normal or abnormal), 4) renal parenchymal echogenicity (normal or abnormal), 5) ureteral dilation (present or absent), 6) bladder abnormality (present or absent), 7) oligohydramnios attributed to urinary abnormality (presence or absence). Notably, the antenatal UTD system also includes recommendations regarding both ongoing prenatal surveillance as well as postnatal workup and treatment depending on grade.

Table 3

	UTD A1	UTD A2-3
APRPD	4 to <7 mm (<28 weeks GA) 7 to <10 mm (≥28 weeks)	≥7 mm (<28 weeks GA) ≥10 mm (≥28 weeks)
		OR
Calyces		Any dilation
		OR
Ureter		Any dilation (with APRPD ≥4 mm or calyceal dilation)
		OR
Parenchyma abnl, bladder abnl or oligohydramnios		Yes (with APRPD ≥4 mm or calyceal dilation)

Adapted from Nguyen HT, Phelps A, Coley B et al. 2021 Update on the urinary tract dilation (UTD) classification system: clarifications, review of the literature, and practical suggestions. Pediatric Radiology; 2022; 52: 740-751

Similar concerns regarding inter and intra-rater reliability have been raised for the UTD system, particularly in the case of peripheral calyceal dilation[32,35] although some studies suggest improved performance in this regard as compared to the SFU[31,36] classification system. While the majority of studies examining the ability of the UTD system to predict clinical outcomes have focused on postnatal classification, there does appear to be good correlation between antenatal (A2-3) and postnatal (UTD P2 or P3) grading. [37] UTD P2 and 3 hydronephrosis are associated with risk of postnatal urinary tract infection, chronic kidney disease, urinary tract abnormalities[38] and need for surgical intervention.[39,40]

3.2 Prenatal management of urinary tract dilation

The diagnosis of urinary tract dilation should prompt a complete ultrasound survey of the urinary tract as well as evaluation of the fetus for co-existing abnormalities including amniotic fluid volume. Identification of female gender is of particular importance in the setting of concern for lower urinary tract obstruction in order to exclude the possibility of posterior urethral valves (as discussed in detail Lower Urinary Tract Obstruction section below). Prenatal urinary tract dilation and amniotic fluid volume can typically be monitored through serial ultrasonography alone. A fetus with a solitary kidney with an accompanying renal abnormality, bilateral moderate to severe hydronephrosis or hydroureteronephrosis, bladder abnormalities and/or low amniotic fluid volumes warrants increased frequency of monitoring. [41]

While prenatal intervention may be considered in cases of lower urinary tract obstruction, prenatal intervention, including early delivery, is rarely indicated in the case of isolated upper urinary tract dilation due to the potential for complications related to prematurity.[42,43]

3.3 Postnatal considerations

Postnatal management of upper urinary tract dilation is covered in more depth in the **hydronephrosis and hydroureteronephrosis section** of the AUA Core Curriculum. Both continuous antibiotic prophylaxis and circumcision may be considered postnatally in order to decrease the risk of urinary tract infection in infants with urinary tract dilation. However, the absolute risk reduction of each of these interventions is not well characterized.

4. Lower Urinary Tract Obstruction

Lower urinary obstruction (LUTO) represents a heterogenous group of congenital abnormalities, ranging from posterior urethral valves to urethral atresia or the rare anterior urethral valves. It is more commonly seen in male fetuses. In female fetuses, the etiology is more commonly secondary to urethral atresia, prolapsing ureterocele or a persistent cloaca. Regardless of the etiology, the obstruction leads to lower and upper urinary tract dilation as well as impaired renal function. The obstruction leads to life-long changes of both bladder and renal function and can sometimes lead to end-stage renal disease. LUTO affects 2-3 in 10,000 live births, although the incidence might be higher due to either elective pregnancy termination or in utero fetal demise. [44]

4.1 Prenatal diagnosis

LUTO is diagnosed on prenatal US. Severe cases are often diagnosed during the first trimester, but the majority are diagnosed during the second trimester at time of the anatomy scan. Classic ultrasound findings of LUTO are a dilated bladder (megacystis) and bilateral hydroureteronephrosis.

In males, the posterior urethra is also dilated, generating the classic key-hole sign. However, this sign is not specific to posterior urethral valves.[45] While it is almost always seen at some point on prenatal imaging in fetuses with valves, 40% of patients with a diagnosis other than posterior urethral valves can also exhibit such sign.

In females, especially in the setting of a cloaca anomaly, prenatal ultrasound can detect a pelvic cystic structure (which can be bilobed). This structure consists of a dilated vagina and uterus. Indeed, in a cloaca with a long common channel, the urine preferentially drains into the vagina and uterus (hydrometrocolpos). In the first trimester, the urine exits the uterus via the fallopian tubes, causing fetal urinary ascites. Later in the gestation, the fallopian tubes occlude, possibly from irritation, and can worsen the hydrometrocolpos, hydroureteronephrosis and oligohydramnios.[46]

Depending on the severity of the obstruction, the kidneys might appear hyperechoic, with sub-cortical cysts and in the most severe cases dysplastic. In the most severe cases, mild pelviectasis with a mildly distended thick-walled bladder and a key hole sign could signify intrauterine renal failure.[47] Eventually, the lack of urine excretion secondary to the LUTO leads to oligo- or anhydramnios and subsequent pulmonary hypoplasia and Potter sequence.

Occasionally, in male fetuses with LUTO, prenatal ultrasound can detect ascites or peri-renal urinomas. This can be seen in up to 20% of cases, and this finding strongly correlated to an improved post-natal renal function outcome, secondary to a pop-off mechanism that relieves intra-renal pressures.[48]

4.2 Prenatal counseling

LUTO stage	I	II	III	IV
Fetal renal anatomy	Normal kidneys or bilateral hydronephrosis	Hyper-echogenic kidneys and/or bilateral hydronephrosis	Hyper-echogenic kidneys ± cysts or dysplasia	Hyper-echoic kidneys + cysts and dysplasia
Fetal urine electrolytes	Favorable	Favorable	Unfavorable	Unfavorable
Amniotic fluid volume (after 18 weeks of gestation)	Normal	Oligohydramnios or anhydramnios	Oligohydramnios or anhydramnios	Oligohydramnios or anhydramnios
Management	No fetal intervention	Vesicoamniotic shunting or fetal cystoscopy	Vesicoamniotic shunting + serial amnioinfusion	Palliative treatment or serial amnioinfusion

Figure 2: Table from Ibirogba ER et al, Prenat Diagn 2020:40(6):661-668.[44]

If there is a suspicion of LUTO, it is recommended that the expecting mother seeks care at an advanced fetal center. Ideally, the fetus would undergo a full anatomical ultrasound, with fetal echocardiogram, to assess for other abnormalities. The fetus should also undergo gender assessment and genetic evaluation, since 20-30% of these patients have underlying genetic abnormalities.[49]

In addition, a fetal urine sample obtained under ultrasound guided vesicocentisis should be collected to assess urine electrolytes. The results of the fetal urine analysis, together with the volume of the amniotic fluid and ultrasound findings, has been used to create a risk stratification model that correlates with postnatal survival (Ruano staging system). [50]

Between the 18th and 30th week of gestation, fetal urine can be sampled and tested for the concentrations of sodium, chloride, calcium, β-2 microglobulin as well as osmolality. There is still a lot of controversy surrounding which are the optimal cut-offs and combinations of fetal urine markers. [51] Usually, a fetal urine sodium <100 mEq/L, chloride <90 mEq/L, osmolality <200 mOsm/L and β-2 microglobulin <6 mg/L are considered favorable indices. Interestingly, a value β-2 microglobulin >13 mg/L was associated with almost 100% risk of neonatal mortality, while levels <6 mg/L were both associated with worse renal function but also increased benefit from prenatal intervention.

Families should be counselled with regards to prognosis and ideally meet with pediatric specialists such as a maternal-fetal specialist, a urologist, and a nephrologist. Prenatal evaluation as well as delivery and postnatal care should take place in a tertiary care center with experience in this patient population.

Based on the gestational age and the fetal prognosis, families should be offered termination or interventions. For mild cases, expectant management is preferred. For moderate cases, there are three main interventions that can be offered to the families.

4.2.1 Vesicoamniotic shunting

Vesicoamniotic shunting is performed percutaneously and involves placement of a double pig-tail catheter with one end in the fetal bladder and the other in amniotic cavity. A recent large randomized European trial (PLUTO trial)[52] compared the outcomes of shunting to conservative management on survival at 28 days after birth. The recruitment goal was 150 patients, but it was terminated after 31 women were recruited due to difficulties in accruing patients. Sixteen women were randomized to intervention and 15 to conservative management. In each group, 12 pregnancies were carried to term. In the intervention group, there was one intra-uterine death after shunting and 3 terminations, while in the conservative group, there was one intra-uterine demise and 2 terminations. Half the patients in the intervention group passed away before 28 days, compared to three quarters of the conservative management arm. All deaths were secondary to pulmonary hypoplasia. There were 7 complications in the shunted patients: 3 spontaneous rupture of membranes, 3 dislodgments and 1 shunt blockage. Unfortunately, the sample size was too small to allow to draw significant conclusions.

4.2.2 Fetal cystoscopy with valve ablation

Fetal cystoscopy is performed percutaneously as well; the scope is introduced through the fetal bladder and the ablation, unlike the one carried out postnatally, is performed in an antegrade fashion, using hydrodistension, a guide wire or a laser. This procedure is considered experimental and carries the same risk of other fetoscopic procedures (37% risk of premature rupture of membranes and 25%

risk of extreme prematurity). [53]

4.2.3 Fetal vesicostomy

Fetal vesicostomy is performed via open fetal surgery, and it is still experimental.[53]

4.3 Immediate postnatal care

The baby should be delivered in a tertiary care center. First, the baby's pulmonary status should be promptly assessed. Second, a catheter should be placed in the bladder for drainage. In the case of urethral atresia, a suprapubic catheter placement or a vesicostomy should be promptly performed.

Once the bladder has been drained, renal ultrasound should be performed, and the patient's renal function should be assessed with serial creatinine. If prenatal imaging is not convincing of LUTO, or if the hospital were the baby is delivered does not offer VCUG, it is acceptable to obtain an US after birth, as long as the baby is making adequate urine. However, in cases of LUTO with poor kidney morphology on prenatal US, and/or in babies with poor respiratory function, renal/bladder US should not delay bladder drainage by foley to prevent further deterioration of the clinical picture.

Urology and nephrology should be consulted. Until a diagnosis of obstruction is confirmed, the baby should be on antibiotic prophylaxis. Once stable enough, a voiding cystourethrogram should be performed to confirm the diagnosis. For girls with cloaca anomaly and hydrometrocolpos, intermittent catheterization of the vagina should be initiated. In these patients, when the catheter is inserted in the opening of the common channel, it always preferentially drains the vagina, and it is impossible to advanced it into the bladder. In case the catheterization is not able to drain the vagina, a decompressing vaginostomy or vaginal tube should be considered. Finally, in all cases of patients with imperforate anus (such as females with cloacal malformation) general surgery should be consulted for diverting colostomy and mucous fistula creation.

Surgical and medical management of LUTO is described in the dedicated AUA Core Curriculum section Posterior Urethral Valve and Other Urethral Obstruction.

5. Myelomeningocele

Myelomeningocele is a neural tube defect that is characterized by failure of the neural tube to close with associated extrusion of the spinal cord into a meningeal sac. Periconceptional folic acid supplementation decreases the risk of neural tube defects, including myelomeningocele[54,55] and has led to mandatory folic acid fortification of dietary grains in the United States. Despite this, the incidence of myelomeningocele is estimated to be 3.4 per 10,000 live births. [56] Myelomeningocele may be diagnosed prenatally through maternal serum alpha fetoprotein levels (AFP) and 2nd trimester screening with ultrasound. Universal screening is supported by both the American College of Obstetrics and Gynecologists (ACOG)[57] as well as the American College of Medical Genetics and Genomics.[58]

The neurologic consequences of myelomeningocele are hypothesized to be related to 'two-hits.' The 'first hit' is the primary developmental abnormality that causes the neural tube defect. The 'second hit'

is due to inflammation and trauma of the exposed spinal cord. There is a wide spectrum of disease phenotypes among patients with myelomeningocele however, abnormalities in bowel and bladder function are common (see AUA Core Curriculum Section on **Spina Bifida and Neurogenic Bladder**).

5.1 Prenatal counseling and evaluation

Neural tube defects are associated with co-occurring anatomic anomalies in 16-26% of patients.[59,60] As such, a complete fetal anatomic ultrasound survey should be performed following positive screening. While not required, fetal MRI may be a useful adjunct when ultrasound imaging is either inadequate for diagnosis[61] or to assure the absence of additional abnormalities when prenatal repair is being considered.

Patients with neural tube defects are also increased risk for associated chromosomal abnormalities. A case series of more than 200 patients demonstrated the risk of concomitant chromosomal abnormality to be 6.5%. For those with myelomeningocele, the rate was 10%.[62] Due to the risk of associated genetic abnormalities, genetic evaluation by amniocentesis for chromosomal microarray should be recommended.[63]

In the setting of an isolated neural tube defect, families may be offered three care options. These include prenatal surgical repair, postnatal surgical repair and pregnancy termination. Pregnancies are typically delivered at term except following prenatal closure (see below) or in the setting of rapidly increasing ventriculomegaly, so that a ventriculoperitoneal shunt may be placed[63]

5.2 Prenatal repair

Prenatal ultrasound imaging suggesting progressive neurologic changes through gestation[64,65] along with animal studies demonstrating preservation of neurologic function after prenatal coverage[66] have led to interest in prenatal surgical repair. Prenatal repair may be considered when there is isolated myelomeningocele in an uncomplicated singleton pregnancy with a normal microarray.[67]

The Management of Myelomeningocele Study (MOMS) was a prospective randomized clinical trial that compared postnatal repair of myelomeningocele to prenatal closure in the second trimester. The trial was stopped for efficacy of prenatal surgery after including 183 of a planned 200 patients. Pregnancy complications including preterm delivery, oligohydramnios, placental abruption and membrane rupture were more common in the prenatal surgery group. The rate of hysterotomy dehiscence (either partial or complete) was 13% after prenatal repair. Rates of perinatal death were the same in both groups [68] however, data supported decreased need for ventriculoperitoneal shunting after prenatal closure (40% in the prenatal repair group versus 82% in the postnatal group), decreased rates of hindbrain herniation and improved lower extremity function.[68,69]

Urologic outcomes from the MOMS population were reviewed at 12 and 30 months of age and failed to demonstrate a difference in need for clean intermittent catheterization (CIC). Notably, need for CIC was determined by independent review of urodynamic and radiographic data that demonstrated bladder or renal abnormalities or in the setting of recurrent urinary tract infections. [70] Similar results

with regards to urologic outcomes have been reported in case-control studies.[71,72]

Longer term urologic data from the MOMS patient population was subsequently reviewed at a mean age of 7.4 years. Outcomes were less stringent (dictated by the treating provider) however there was a statistically significant difference between CIC rates among the prenatal versus postnatal group (62 vs 90%) as well as volitional voiding (25 vs 4%). There were also fewer patient's taking anticholinergic medications in the prenatal group. Number of surgical procedures (including augmentation cystoplasty or vesicostomy) and urodynamic and ultrasound data [73] where similar between the two groups. The etiology and significance of these follow up results is unclear.

In 2017, the Committee on Obstetric Practice Society for Maternal-Fetal Medicine recommended that prenatal repair should be offered only to carefully selected patients at facilities with 'appropriate level of personnel and resources.'[67] Notably, late-preterm to early-term delivery (before 37 weeks) is indicated if in utero fetal surgery has been performed because of the increased risk of uterine rupture. [63]

5.3 Team of providers

Positive prenatal screening for a neural tube defect should prompt referral to an experienced spina bifida provider team for counseling regarding possible fetal intervention, postnatal management and prognosis. Involvement of maternal-fetal medicine, pediatric neurosurgery, pediatric urology, neonatology and genetics should be considered.

6. Bladder and Cloacal Exstrophy

Bladder and cloacal exstrophy are congenital malformations that are part of a spectrum of anterior abdominal wall malformations, including umbilical hernias, gastroschisis and omphalocele as well. Each year classic bladder exstrophy affects 1 in 30,000 live births[74] and cloaca exstrophy involves 1 in 200,000 to 400,000 live births.[75,76] Of the two, cloaca exstrophy represents the most severe phenotype.

For more information on treatment of bladder exstrophy and cloaca exstrophy, please refer to the dedicated AUA Core Curriculum Section: **Exstrophy**.

6.1 Prenatal diagnosis

Bladder and cloacal exstrophy are usually suspected when the bladder is not seen filling on pre-natal ultrasound. The fetal bladder can be visualized after the 13th week of gestation.[77] Since the fetal bladder cycles frequently, every 15-20 minutes or so, variations of bladder volume, even on one ultrasound study, are to be considered normal. If a bladder is not identified, it is important to identify the presence of normal kidneys, since bilateral renal agenesis would also present with an empty bladder, but it would also be associated with low amniotic fluid levels. [78] In the setting of cloaca exstrophy, unilateral renal agenesis is not an uncommon finding.

Other findings on prenatal ultrasound can be suggestive of bladder exstrophy, such a lower abdominal protrusion (due to pressure of other abdominal viscera on the bladder plate, usually seen

later in pregnancy), a low insertion of the umbilical cord, a diminutive phallus in case of a male fetus, and lateral splaying of the iliac crests.[79] These findings can be hard to detect since they are affected by fetal positioning at time of the ultrasound.

The bladder is not documented in 70 to 90% of fetuses with bladder or cloacal exstrophy.[79,80] Therefore, if other findings suspicious for exstrophy are identified, the presence of the bladder should be carefully assessed. Sometimes, urachal remnants can be seen mimicking the bladder, but unlike a bladder, they do not cycle. One finding suggestive of cloacal exstrophy is the elephant trunk sign, which is secondary to the intussuscepted ileum protruding at the level of the bladder plate.

Cloacal exstrophy are associated with other congenital malformations, unlike classic bladder exstrophy. Therefore, presence of anomalies such as omphalocele, myelomeningocele, cardiac and abnormalities, and limb deformities, are suggestive of a diagnosis of cloacal exstrophy.

More recently, the use of pre-natal MRI has been studied[81] to improve diagnosis of bladder and cloacal exstrophy. While a fetal MRI performed better than a fetal US, it still misdiagnosed 10% of the cases of simple bladder exstrophy as cloacal exstrophy, mainly because the bladder plate was protruding anteriorly, with bowel loops right behind it, simulating an omphalocele. However, both MRI and US were able to correctly identify the insertion of the umbilical cord, confirming the diagnosis of classic bladder exstrophy. Indeed, the umbilical cord always inserts superior to the bladder plate in a classic exstrophy, while it inserts in the middle of the omphalocele defect.

6.2 Prenatal counseling

Average gestational age of diagnosis in the literature ranges from 14 to 30 weeks,[77,82] with the majority being diagnosed after 24 weeks of gestation, the limit for fetal viability. The survival of neonates with classic bladder and cloacal exstrophy nowadays exceeds 90%. [80,83]

Two main issues are important to discuss at prenatal counseling, the first being discussing the functional prognosis of the child, and the second the establishment of a postnatal plan. With regards to functional outcome of classic bladder exstrophy, much depends on the size of the bladder plate and on the gender of the child. Parents should be counseled on the need for multiple surgeries first to reconstruct the bladder, other surgeries to reconstruct the genitalia and finally surgeries address vesicoureteral reflux and urinary continence. Parents should also be warned that their child might have to rely on intermittent catheterization to achieve dryness.

In the setting of cloacal exstrophy, parents once again must be counseled on the need of multiple surgeries, starting in the first few days of life, since these patients require colonic diversion and creation of a mucous fistula. Further counselling should involve not only urinary function, but also bowel function and the need for future surgeries as well as the likelihood of persistent colostomy or bowel regimens. For both types of conditions, parents should be counseled on the future on their child sexual quality of life. While for female patients the sexual outcome is promising, male sexual function is still a challenging subject.

Lastly, the neurological outcomes of patients with cloacal exstrophy and myelomeningocele should

be addressed.

6.3 Immediate postnatal care

Delivery should be planned to happen in a tertiary care center with available pediatric urology and general surgery, and ideally a center that has experience in managing this patient population.

Once the baby is born, if the diagnosis of classic exstrophy is confirmed, no further imaging is required. A renal ultrasound can be obtained to assess normalcy and patency of the upper urinary tract. The bladder should be protected with non-stick plastic wrap until the surgery for bladder closure is performed. The plastic wrap should be exchanged with every diaper change and the bladder mucosa should be irrigated with saline. [84]

If the baby has cloacal exstrophy, they should undergo diverting colostomy and mucus fistula in the first few days of life. Furthermore, full assessment of other congenital abnormalities should be assessed with a cardiac echo as well as a spinal and renal ultrasound.

7. Differences of Sex Development

Historically, differences of sex development (DSD) have been identified postnatally. Prenatal diagnosis of DSD may occur through 1) detection of genital abnormalities on ultrasound, 2) genetic testing demonstrating sex chromosome aneuploidy or 3) discrepancy between genetic and phenotypic (ultrasound) sex, so-called genotype-phenotype discrepancy. Recent published studies suggest prenatal detection rates of 15-24%[85,86] however, due to improving imaging technology and more widespread use of genetic tools, prenatal detection may be becoming more common.

7.1 Prenatal imaging of the genitalia and reproductive structures

Phenotypic fetal sex can be detected through ultrasound imaging as early as the first trimester and with increasing accuracy with advancing gestational age.[87,88] At 12 weeks gestation, the angle of the pubic tubercle, or ‘sagittal sign’ may be used to infer phenotypic sex. In this case, a more downward (or obtuse angle) is consistent with female while a more upward (or acute angle) is consistent with male phenotypic sex.[89]

Later in pregnancy, assignment is based on direct visualization of the genital anatomy. Specifically, phenotypic female sex is designated by identification of the labial folds and clitoris and after 19 weeks gestation, the uterus. In contrast, phenotypic male sex is designated by identification of the scrotum, penis and after 25 weeks gestation, descended testes. [90]

Genital abnormalities on prenatal ultrasound but may indicate the presence of a DSD however, the differential diagnosis is broad and includes isolated genital anomaly (e.g., hypospadias), intra-uterine fetal growth restriction, chromosomal abnormality, anomaly of steroid biosynthesis, androgen insensitivity and abnormality in fetal development (including bladder or cloacal exstrophy). Determination of genetic sex either by cfDNA or karyotype is almost always beneficial when genital ambiguity on ultrasound is recognized. Once chromosomal abnormalities and exstrophy are excluded, consideration should be given to steroid profiling or in a 46,XY fetus, sequencing of the

androgen receptor gene to exclude androgen insensitive syndromes.[89]

7.2 Genetic testing

Traditionally, genetic sex is established by quantitative fluorescent polymerase chain reaction (qfPCR) or FISH of either amniocytes or chorionic villi following amniocentesis or chorionic villus sampling (CVS) respectively. Genetic testing allows for accurate diagnosis of sex chromosome aneuploidy however, both amniocentesis and CVS are associated with risks to the mother and fetus. [1] including a miscarriage rate of 0.5-1% even in experienced hands.[91]

Cell free-DNA (cfDNA) identifies placental cell-free DNA from the cytotrophoblast in the maternal circulation via blood draw. Testing can be performed after 10 weeks gestation when the mean 'fetal fraction' is approximately 10%.[92,93,94] In the case of cfDNA, genetic sex is determined by detecting signal from Y-chromosome sequences in the maternal plasma, including SRY, DYS14 and amelogenin. [95] While cfDNA screening represents minimal risk to the mother and fetus, recent studies have demonstrated positive predictive values of only 35-58% for sex chromosome aneuploidies, with particular poor performance in the case of monosomy X (21%).[96,97]

7.3 Genotype-phenotype discrepancy

Genetic sex as determined by prenatal screening/testing may be discordant from genital anatomy on prenatal ultrasound. This is termed genotype-phenotype discrepancy. More widespread use of cell-free DNA (cfDNA) has led to an increase in detection of prenatally diagnosed genotype-phenotype discrepancy[98]

Notably, genotype-phenotype discrepancy may be caused by a wide variety of phenomena. In addition to a DSD, clinicians should consider the possibility of lab errors, fetoplacental mosaicism, undetected twin pregnancy and/or twin demise, history of organ transplantation in the mother from a male donor or maternal malignancy. [98] Genotype-phenotype discrepancy detected through cfDNA should be confirmed through karyotype by amniocentesis. Determination of parental karyotype may also be considered in this setting. [98] Targeted molecular testing for rare DSD conditions in the absence of a family history has been shown to be low yield but may become more promising with advances in sequencing techniques.[99]

7.4 Prenatal management of congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders that are due to abnormal cortisol synthesis. The most common form is caused by mutations in CYP21A2, the gene that encodes the 21-hydroxylase enzyme. Abnormal 21-hydroxylase function results in impaired glucocorticoid and mineralocorticoid production leading to excess ACTH secretion (due to failed negative feedback mechanisms) and overproduction of adrenal androgens (for details of steroid biosynthesis pathway, see figure 1 in the AUA Core Curriculum section: **Disorders of Sexual Differentiation**). Newborn screening programs routinely incorporate testing for 21-hydroxylase abnormalities due to associated aldosterone deficiency. Prenatally, excess adrenal androgen can

result in virilization of female genitalia.

Prenatal diagnosis of CAH is limited almost exclusively to families where there is a previously affected child. Families with affected first degree relatives should be offered genetic counseling due to the 1:4 associated risk in offspring. Less commonly, CAH may be diagnosed in the context of abnormal genitalia at the time of anatomic scan in a genetic 46,XX fetus.[89]

Prenatal treatment of CAH is directed at minimizing genital virilization in the female fetus. Advocates of prenatal treatment also promote the theoretical advantage of decreased androgen effect on the developing female brain however, this has not been adequately studied. Although the mechanism of action is unclear in the fetus, [100] dexamethasone treatment suppresses fetal ACTH resulting in decreased androgen levels *in utero.* Virilization of the female fetus begins 6 weeks after conception therefore, for maximal efficacy dexamethasone must be initiated as soon as pregnancy is established. Notably, this is prior to diagnosis of CAH and prior establishing fetal genetic sex thereby exposing 7 out of 8 patients to unnecessary treatment. Published studies of the effectiveness of prenatal dexamethasone are limited. The largest series includes 25 CAH-affected females who received dexamethasone before the ninth week of pregnancy. The mean Prader score for the treated group was 1.0 vs. 3.7 among those who were untreated. [101]

Documented side effects in the mother of weight gain[101] and the potential for teratogenic effects in the fetus,[102,103,104] informed the 2010 Endocrine Society Clinical Practice Guidelines that indicate that prenatal therapy for CAH should 'be regarded as experimental' and limited to 'protocols approved by Institutional Review Boards at centers capable of collecting outcomes data.' [100]

7.5 Impact of prenatal detection of differences of sex development

The psychosocial implications of prenatal detection of DSD should not be underestimated. Distress, anxiety and depression are commonly described by families being evaluated prenatally for DSD.[86] Families may express concerns regarding potential limitations in quality of life related to a DSD diagnosis for their child.[86] Worries about such diverse topics as the stress and burden of medications and procedures, long-term body image and difficulties with navigating medical systems have also been commonly described. [105] Despite this, a majority of families whose child is found to have sex chromosome aneuploidy describe early diagnosis as having a positive impact on their child's life. [106]

7.6 Team of providers

Due to both the medical and psychosocial complexity associated with prenatal diagnosis of DSD, families may benefit from consultation with providers who possess a range of expertise. This includes urology, endocrinology, genetic counselor/medical geneticist, social work, psychology and DSD patient advocate.

8. Structural Abnormalities of the Kidneys

Structural abnormalities of the kidneys may be identified prenatally on screening ultrasound. Concern for a structural abnormality of the kidney should prompt a detailed anatomy scan to look for any

associated anomalies and generally, karyotype should be offered in the case that additional anomalies are identified.[107] Structural kidney diseases as described below rarely require surgical intervention except where there are associated genitourinary conditions and are often managed in coordination with pediatric nephrology.

8.1 Abnormalities in kidney number

Renal agenesis is the congenital absence of the kidney. Bilateral renal agenesis is a life-limiting condition except with serial amnioinfusions[108,109] that aim to correct anhydramnios and support lung development. The Renal Anhydramnios Fetal Therapy (RAFT) study is an experimental treatment for mothers and their babies affected by renal anhydramnios that is ongoing.

In contrast, unilateral renal agenesis (URA) occurs with an incidence of 1 in 1000 live births.[107] In the case of isolated URA, there is no need for prenatal treatment or intervention as renal function and amniotic fluid levels are typically normal. URA is characterized by an empty renal fossa on screening ultrasound.

Abnormalities of the contralateral renal unit are seen in approximately one third of patients with vesicoureteral reflux being the most common finding.[110] In female patients, Mullerian abnormalities may also be identified in up to one third of cases.[111,112] In males, Wolffian duct abnormalities are commonly identified.[113,114] The risk of a genetic syndrome in association with renal agenesis has been estimated to be as high as 30%.[115]

8.2 Abnormalities in kidney location

The fetal kidney ascends from the renal pelvis to the retroperitoneum by nine weeks gestational age. When the kidney fails to complete this ascent process normally, it is referred to as ectopic. An ectopic kidney may be identified in the pelvis, abdomen or less commonly in the thorax. Additionally, the kidney may be termed ‘crossed’ when it is located ipsilateral to the normal kidney.

Renal ectopia is frequently accompanied by abnormalities of renal rotation. The renal pelvis in an ectopic kidney is often located anterior to the renal parenchyma rather than medial as is typical. Hydronephrosis is commonly observed in ectopic kidneys and may be due to renal malrotation however, obstruction and vesicoureteral reflux should be ruled out postnatally in the case of significant renal dilation or concerning clinical symptoms due to the increased risk of these abnormalities in ectopic kidneys.[116] As with abnormalities in renal number, renal ectopia is associated with increased risk of anomalies of the reproductive structures in both males and females.[117,118]

8.3 Fusion abnormalities

Horseshoe kidney is the most common renal fusion anomaly. This occurs when there are two distinct renal units on either side of the midline that are connected by a fibrous isthmus. Affected kidneys are typically found in the pelvis or at the lower lumbar vertebral bodies. Hydronephrosis has been detected in up to 80% of horseshoe kidneys.[119,120] As described above with ectopic kidneys, rotational abnormalities may account for some instances of observed renal dilation however

horseshoe kidneys are known to exhibit increased rates on congenital anomalies. Specifically, the rate of vesicoureteral reflux is estimated at 10-25% [121,122] while ureteropelvic junction obstruction may be seen in as many as 23% of patients.[121] Notably, individuals with horseshoe kidney are also at increased risk for nephrolithiasis.[123]

Horseshoe kidneys are associated with genetic disorders including turner syndrome, trisomy 13,18 and 21.[124] Data from the National Wilms Tumor Study suggests that individuals with horseshoe kidneys may also be at increased risk for Wilms tumor.[125]

8.4 Cystic kidney disease

Polycystic kidney disease is the most common heritable kidney disease. Autosomal dominant polycystic kidney disease (ADPKD) presents most commonly in the fifth to sixth decades of life however, prenatal diagnosis may occur in 2-5% of cases.[126] Family history or molecular diagnosis is required to differentiate ADPKD from autosomal recessive polycystic kidney disease (ARPKD). If ADPKD is suspected, prenatal evaluation with renal ultrasound and genetic counseling is recommended.[127]

Autosomal recessive polycystic kidney disease is less common than ADPKD. It is often diagnosed prenatally due to the fact that affected kidneys appear large and echogenic on ultrasound[128] as early as the second trimester.[129] There is typically also associated oligohydramnios due to decreased renal function. Molecular genetic analysis is the only way to accurately diagnosis ARPKD prenatally.[127] Perinatal mortality has been reported in 20-30% and as such, the option of pregnancy termination may be considered.[127,130] Due to the complexity of diagnosis and care of a fetus with ARPKD, an experienced multidisciplinary team should be consulted including genetics, neonatology and nephrology.

Multicystic dysplastic kidney (MCDK) has an incidence of 1 in 4300 live births.[129] It may be confused for severe hydronephrosis with associated cortical thinning (UTD P3 or SFU grade 4 hydronephrosis). MCDK is typically sporadic[131] and in contrast to a severely hydronephrotic kidney, affected units are nonfunctional. The exact cause is unknown but MCDK is postulated to result from early, severe obstruction. MCDK is associated with increased risk of urinary tract infection and hypertension postnatally.[132] Vesicoureteral reflux,[133] ipsilateral ureterocele[134,135] and contralateral ureteropelvic junction obstruction[136] have been demonstrated to be associated with MCDK however, screening for these entities is not generally recommended unless there is clinical concern.

9. Abdominal Masses

Abdominal masses that are diagnosed in utero are extremely rare but should be diagnosed accurately to plan prompt treatment after birth. Masses can originate from several organs. Most of them, close to two thirds, arise from the kidney, and the majority of them are benign,[137] consisting of hydronephrotic or cystic kidneys. For the interest of the chapter, we will focus primarily on renal masses.

The most common renal mass diagnosed prenatally and in newborns is congenital mesoblastic nephroma (CMN). This is most commonly diagnosed in the first 3 months of life. When diagnosed prenatally, they are associated with polyhydramnios 70% of times.[138]

The differential diagnosis of CMN is Wilms tumor, since they are indistinguishable on imaging. Other even rare renal malignancies are rhabdoid tumor, clear cell sarcoma, renal cell carcinoma and ossifying renal tumor of infancy.

Among patients with predisposing syndromes for Wilms, nephroblastomatosis can be detected as multifocal renal nodules. These nephrogenic rests are better diagnosed on cross sectional imaging.[139] Renal vein thrombosis can simulate a renal mass by causing venous congestion and hemorrhage. Risk factor for renal vein thrombosis are polycythemia and diabetic mother.

Lastly, adrenal masses can also be diagnosed on prenatal US. Adrenal hemorrhage, which is triggered by perinatal asphyxia, sepsis, coagulopathy and perinatal trauma, is often diagnosed prenatally, and it has to be differentiated from neuroblastoma. The latter has evidence of vascularity and calcifications on ultrasound.[140] More rare prenatal lesions are adrenal adenomas or carcinomas. These masses are usually associated with hormonal imbalances.

If a renal mass is suspected on prenatal ultrasound imaging, urologist should counsel the family on post-natal management as well as on differential diagnosis. Families should be reassured that the majority of these masses in infants are benign. Once the baby is delivered, post-natal imaging should be obtained. If a renal mass is still highly suspected, timely radical nephrectomy, through an open approach, should be performed to confirm the diagnosis. Often, surgical resection is the definitive treatment as well. For more information about pediatric renal malignancies, please refer to the respective AUA Core Curriculum Section: **Genitourinary Oncology**.

Presentations

Prenatal Consultations Presentation 1

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