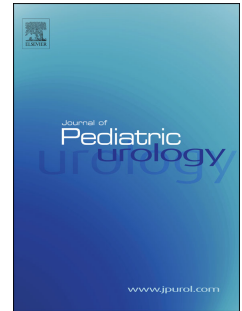


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leveraging early detection to prevent complications

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EDUCATIONAL ARTICLE

Screening for Mullerian anomalies in patients with unilateral renal agenesis: leveraging early detection to prevent complications

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Summary Background: Mullerian anomalies have a known association with renal agenesis yet, to date, there are no formal recommendations for screening women with certain renal anomalies for associated genital tract disorders.

Objective: The objective of this study is to review current data regarding the association between renal and Mullerian anomalies, and propose screening recommendations.

Study design: A comprehensive review of the literature was performed to identify relevant articles using the keywords “unilateral renal agenesis,” “renal anomalies,” and “Mullerian anomalies.”

Results: Over 30% of patients with unilateral renal agenesis have an associated Mullerian anomaly. However, diagnosis is frequently delayed in this population until after menarche when complications of retrograde menstruation with obstructive anomalies lead to significant problems including endometriosis, pelvic inflammatory

disease, and infertility. No clear guidelines exist for communication among the antenatal sonographer, the obstetrician, the parents, and the child's pediatrician, which creates a barrier to effective screening and follow-up. Further, no current guidelines exist for screening women with certain renal anomalies for Mullerian anomalies.

Discussion: The complications of Mullerian anomalies are easily preventable if identified early. We propose new guidelines for education and screening for Mullerian anomalies in patients with unilateral renal agenesis (URA) and multicystic dysplastic kidney (MCDK) to guide providers, patients, and parents on proper identification and management (Table).

Conclusions: Screening young women with URA and MCDK for Mullerian anomalies has the potential to prevent long-term complications from untreated obstructive malformations. Identification of unilateral renal agenesis on antenatal ultrasound must be clearly articulated with parents and the child's pediatrician so that proper screening can be performed before menarche. Pelvic sonography is a low-cost, high-yield screening tool to identify these anomalies.

Table. Recommendations for screening and management in female infants born with unilateral renal agenesis

Antenatal	Involved specialty Maternal fetal medicine General obstetrician	Screening Antenatal ultrasound (identify renal agenesis)	Management Parental counseling: importance of follow-up, screening before menarche
Infancy	Pediatric urology	Physical exam Follow-up US (1 month) Consider VCUG	Parental counseling: screening before menarche
After telarche and before menarche	Pediatrician Pediatric urology Obstetrics/gynecology Adolescent GYN (if available)	Pelvic US → If abnormal, three-dimensional US vs. MRI	Correct obstructive anomalies

KEYWORDS

Unilateral renal agenesis;
Mullerian anomalies

Introduction

Although the association between Mullerian and Wolffian anomalies is well classified, to date, no formal recommendations exist for screening female patients with known renal anomalies for concomitant anomalies of the genital tract. While renal anomalies are frequently identified on routine antenatal ultrasonography surveillance, Mullerian anomalies are most commonly only identified once a patient experiences complications of the underlying disorder such as endometriosis, pelvic inflammatory disease, or infertility. In this review, we delineate the relationship between Mullerian and Wolffian development, explore the diagnosis of anomalies as well as the consequences of failed diagnosis. Finally, we review appropriate management of these disorders, and make recommendations for screening all patients with known renal anomalies for Mullerian anomalies.

Embryology

The development of the genitourinary system is a complex interaction between the Mullerian and Wolffian ducts. Prior to sex differentiation, the urogenital ridge gives rise to the primordial gonads, which in XY individuals, release SRY leading to male differentiation. This ridge gives rise to the Wolffian ducts, which at 6 weeks induce invagination of the dorsal coelomic epithelium, forming the Mullerian ducts [1]. In females, the paired Mullerian ducts undergo full differentiation by 7 weeks and then elongate and canalize in a cranial to caudal fashion [1,2]. Between 10 and 12 weeks, the Mullerian ducts undergo fusion beginning in the midline and extending in a cranial-caudal direction. Distally, the ducts fuse with the urogenital sinus at the Mullerian tubercle. Proximally, the ducts fuse to form the uterus, cervix, and upper two-thirds of the vagina. Greater proliferation at the cranial aspect leads to the classic wedge shape of the uterine body. Once the Wolffian duct contacts the cloaca at the caudal aspect of the embryo, it grows cranially as the ureteric bud until it comes in contact with the metanephric mesenchyme, forming the metanephros. The ureteral buds develop at the intersection of the Wolffian ducts and the urogenital sinus. The ureteric bud and

metanephric mesenchyme, via mutual induction, initiate growth, forming the kidney. Urogenital structures develop under the control of several signaling genes, including WNT, HOX, and Nodal/Lefty, which through complex pathways lead to formation, patterning, and laterality of structures, respectively [2].

Mullerian anomalies provide some insight into the development of the urogenital system. As classified by Acien in 1992, anomalies can be described by their embryologic origins, with predictable patterns of malformations observed based on the level of insult [3]. Agenesis of the urogenital ridge, Wolffian duct, Mullerian system, cloaca, or the presence of a combination of malformations demonstrate predictable consequences of failed embryologic steps. For example, a patient with complete agenesis of the urogenital ridge will demonstrate ipsilateral renal agenesis and absent Mullerian structures on the corresponding side [4]. This explains the close association between Mullerian and renal anomalies: up to 50% of Mullerian anomalies are associated with some form of renal anomaly, with up to 92-100% in patients with obstructed hemivagina [5,6]. The total number of patients with renal malformations who have Mullerian anomalies is not known; however, some studies have estimated that the prevalence is as high as 100%, although others have reported much lower numbers at 21.7% [4]. It is important to note that many of these studies do not specify which renal anomalies are included in their study, likely explaining at least part of the variation. Although the renal anomalies most commonly associated with Mullerian anomalies are URA and MCDK, unilateral or bilateral pelvic kidney, horseshoe kidney or renal crossed ectopia as well as pyelocaliceal duplicity, ectopic ureter, or bilateral pyelectasis have also been reported [4].

Prenatal evaluation

Ultrasound screening during pregnancy has resulted in the increased detection of renal anomalies including URA and MCDK, the two most common conditions leading to CSFK. Given that the most common associated anomalies of CSFK are urologic, it is important to fully characterize the fetal kidneys, ureters, bladder, and urethra [7-10].

In examining the contralateral kidney, one should note its size, echogenicity of the renal parenchyma, presence of hydronephrosis, and presence of cysts. Increased echogenicity and the presence of cysts are suggestive of renal dysplasia.

Hydronephrosis can result from transient or non-transient physiologic hydronephrosis, obstruction, or VUR. In the setting of renal agenesis, sonography may also reveal flattening of the adrenal gland when the kidney is absent [11]; however, prenatal ultrasound is not a reliable method to screen for genital anomalies associated with CSFK.

Importance of diagnosing Mullerian anomalies (OHVIRA)

The diagnosis of uterine anomalies is frequently fraught with delays and challenges. Uterine anomalies are rarely diagnosed before puberty, and length of time to diagnosis is on average 37.8 weeks from the onset of symptoms, with 100% of patients in one study being incorrectly diagnosed on presentation [12]. Patients most commonly present with dysmenorrhea and irregular bleeding following puberty [13-15]. A less common presentation includes an infant presenting with an abdominal/pelvic mass on antenatal ultrasonography or at birth [16-18]. Another less common presentation includes a patient who presents with an undiagnosed febrile illness secondary to pelvic inflammatory disease (PID) or difficulty conceiving during their reproductive years [13,14]. Obstruction of the outflow of menstrual bleeding, once young women reach menarche, leads to hematometria and eventually efflux of menstrual blood into the peritoneal cavity. Blood collections may become infected leading to pelvic inflammatory disease or abscesses. Endometrial tissue that remains because of the outflow obstruction may implant, leading to endometriosis which can result in cyclic pain. Finally, scarring from the above processes as well as an abnormality of the cavity may contribute to infertility [12,13,19]. These consequences may be prevented through early identification of anomalies and alleviation of obstructing structures through either drainage or definitive surgical management [13].

While pelvic ultrasound, particularly 3-D ultrasound, may be useful for diagnosis, the gold standard assessment is MRI [20]. Laparoscopy may provide additional information about Mullerian structures as well as assist in the diagnosis and management of complications [2,13]. Invasive methods such as hysterosalpingogram are no longer recommended for diagnosis because of their invasiveness and increased radiation exposure. MRI has demonstrated 100% accuracy in detecting Mullerian

anomalies, with excellent visualization of the uterine fundus and pelvic anatomy [4,21]. It remains the diagnostic mainstay for most experts in radiology and gynecology [21-23].

In more recent studies, three-dimensional ultrasound has demonstrated high sensitivity and specificity (93% and 100%, respectively) when performed by experienced sonographers [21,24]. This modality is clearly preferable to more expensive and invasive diagnostic methods; however, it requires a certain level of expertise for accuracy. Other studies have even suggested that three-dimensional ultrasound may have a higher sensitivity and specificity than MRI. Studies of patients with surgically proven Mullerian anomalies have noted a sensitivity of 96-100% and 77-79% for three-dimensional ultrasound and MRI, respectively [25,26]. This suggests that in centers where three-dimensional ultrasound is available, it may be preferable to MRI for diagnosis.

The coexistence of renal, Wolffian, and Mullerian anomalies is well recognized. It is estimated that 30% of patients with URA have reproductive tract anomalies [27]. It is also estimated that uterine anomalies occur in 1 in over 500 females, and of those patients, 43% have URA [28]. The screening and management of these abnormalities in children is not well defined. Renal anomalies are easily diagnosed with ultrasound and commonly diagnosed prenatally. Because of the frequent association with reproductive tract anomalies, we recommend screening all girls between telarche and menarche with CSFK for Mullerian anomalies.

Postnatal evaluation

A complete physical exam along with supporting laboratory studies and imaging should be performed. In males, close attention should be paid to the genital exam, palpating for a normal ipsilateral vas deferens and epididymis. In females, the genital exam should include checking for a vaginal bulge or lower abdominal mass, indicating mucoculpos. If CSFK is diagnosed prenatally, an ultrasound should be repeated within 1 month of life to confirm the diagnosis and further evaluate the contralateral kidney. Although rarely necessary, radioisotope studies using agents such as dimercaptosuccinic acid (DMSA) can be used to confirm the diagnosis of a non-functioning renal unit. The incidence of contralateral VUR has been described in up to 30% of patients with URA, and up to 43% of patients with MCDK [7-9,29,30]. Screening for VUR with a VCUG is

controversial as it raises the dilemma of management of an asymptomatic patient with VUR. Some have advocated for no screening for this condition or selective screening only in the setting of hydronephrosis. However, a voiding cystourethrogram in patients with CSFK is still recommended by most in the setting of CSFK [10,11,27]. The authors recommend a pediatric urologist counsel regarding the option of a voiding cystourethrogram in a patient with CSFK in addition to education regarding signs and symptoms of a urinary tract infection to allow early diagnosis and treatment. In addition, contralateral ureteropelvic junction obstruction has been described with URA in up to 12% of MCDK patients [8]. If there is high-grade contralateral hydronephrosis, a technetium-99m mercaptoacetyltriglycine (^{99m}Tc MAG3) scan should be performed to rule out obstruction.

Long-term considerations

Patients with CSFK should exhibit compensatory hypertrophy of the solitary kidney, which is typically defined as two standard deviations greater than the normal expected mean renal volume or surface area [8,9]. Aslam and coworkers, as part of the Trent and Anglia Multicystic Dysplastic Kidney Study Group, published a large series documenting the natural history of patients with MCDK, reporting complete involution of the abnormal kidney in 33% at 2 years of age, 47% at 5 years, and 59% at 10 years [31]. Although some advocate that patients should be followed with renal ultrasounds until compensatory renal growth is demonstrated in the contralateral kidney, others have advocated for no further ultrasound in the setting of a normal contralateral kidney once the diagnosis of MCDK has been established [32,33].

Representative case presentation

During prenatal screening, a female fetus is found to have URA on the right. The parents are made aware and the suggestion is made to follow-up with their pediatrician after delivery. In the normal newborn nursery, the pediatrician notes it in the medical record and reassures the parents.

The patient begins normal pubertal development of breasts at age 10. At age 12 she has menarche. These menses, initially irregular, are accompanied by severe dysmenorrhea treated with ibuprofen but without full relief. She misses 2-3 days of

school with each period, which becomes monthly after about 4 months. Defecation becomes painful, and an osmotic laxative is recommended for presumed constipation.

At age 13, 1 year after menarche, she presents to the emergency room with intractable pain. A midline pelvic mass is identified and an ultrasound is nondiagnostic. She is treated for pain and referred to a pediatric gynecologist. An MRI is performed 10 days later, which is consistent with an obstructed hemivagina and uterus didelphys. She undergoes resection of her septum. The delay in diagnosis has resulted in missing 3 weeks of school as well as a major dance recital, with significant emotional toll.

Had this patient and her physicians been aware of the association between URA and potential uterine anomalies, time to diagnosis through pelvic sonography could have been significantly shortened. Furthermore, early identification would have allowed for decreased time to treatment and, in turn, less exposure to potential future complications such as endometriosis and infertility.

Discussion

While increased screening may prevent both long- and short-term complications of Mullerian anomalies, it is important to consider potential risks. Mullerian anomalies are uncommon and affect approximately 3-6% of girls [34]. URA is estimated in 1/1000 live births, and in girls who are diagnosed with URA, the incidence of all types of Mullerian anomalies, including but not limited to OHVIRA, is estimated to be 55-70%. The screening of girls with URA for Mullerian anomalies would identify a subset of girls that might be at risk for serious complications.

One must consider the emotional stress patients and parents may experience following education on an overall rare condition. Also, the societal cost of screening should be weighed carefully. In spite of these concerns, the impact of not screening for Mullerian anomalies and resulting delayed diagnosis can be catastrophic to patients. Costs can be limited through serial testing with ultrasound used to identify a subset of patients that could benefit from further screening with three-dimensional ultrasounds or MRI (i.e., after identification of a uterine anomaly). The potential benefits of early diagnosis and surgical correction of OHVIRA outweigh these concerns.

Recommendations

While informal recommendations for Mullerian anomaly screening have been proposed in conjunction with reported cases, there are no formal medical recommendations in place [35]. We propose a two-tiered method for screening females identified with renal anomalies to facilitate earlier diagnosis and prevent long-term complications of untreated Mullerian anomalies.

1. Prenatal: At the time of a fetal anatomy scan, when URA and MCDK are identified, we recommend that the child's parents receive information regarding the possibility of Mullerian anomalies and the need for screening at puberty, in addition to proper renal screening for potential renal complications. Parents should be encouraged to share this information with their daughter's pediatrician to ensure proper surveillance. The obstetrician and antenatal ultrasonography team should share responsibility for communicating this information.
2. Puberty: We recommend that girls with known URA and MCDK undergo imaging with pelvic US, followed by MRI for any abnormal results, at the time of pubertal onset and prior to menarche to prevent short-term complications including cyclic abdominal pain and long-term complications of retrograde menstruation including endometriosis, pelvic inflammatory disease, and infertility.
3. Management: We recommend careful monitoring and early surgical management of girls found to have OHVIRA syndrome that includes vaginal septum excision and drainage of hematocolpos.

Conclusion

Pelvic sonography for patients with a solitary functioning kidney meets all of the criteria for a good screening test: low cost, the potential for early intervention for obstructive Mullerian anomalies, and the prevention of serious late complications. Proper screening requires communication from antenatal identification of a solitary functioning kidney, to postnatal management. Key stakeholders, including maternal fetal medicine specialists, pediatric urologists, obstetrician gynecologists, pediatricians, and parents, will need to identify best practices in sharing information across time and specialties to ensure proper screening in a timely fashion. Through this collaborative effort, we will be able to identify a potentially life altering issue and intervene to prevent future complications.

Conflict of interest

None.

Funding

None.

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1. A 4-year-old female patient with known unilateral renal agenesis presents to your practice to establish care. The risk of having a concurrent Mullerian Anomaly is:
 - a. no additional risk
 - b. 15%
 - c. 30%
 - d. 45%
 - e. 60%
2. A patient with For a patient with complete agenesis of the urogenital ridge, is likely to have which of the following Mullerian anomalies?
 - a. Mayer-Rokitansky Syndrome
 - b. Bicornuate uterus and hydroureter
 - c. Imperforate hymen
 - d. Ipsilateral renal agenesis and absent Mullerian structures
 - e. Duplicate ureter
3. Unilateral renal agenesis is most commonly identified
 - a. during the antenatal ultrasound
 - b. shortly after birth based on voiding patterns
 - c. following urinalysis assessment with pediatrician
 - d. in adulthood
 - e. frequently not identified
4. An 11-year-old girl who has been identified with an obstructive Mullerian Anomaly. She has an increased risk of which of the following
 - a. endometriosis
 - b. infertility
 - c. pelvic inflammatory disease
 - d. endometriosis and pelvic inflammatory disease
 - e. all of the above
5. A newborn is referred unilateral renal agenesis identified on antenatal ultrasonography. The following studies should be performed for all patients within the first month of life
 - a. radioisotope study with DMSA (dimercaptosuccinic acid)
 - b. renal ultrasound
 - c. CT scan
 - d. Urine culture
 - e. Urine cytology
6. A nine-year-old girl is referred to your practice for known renal agenesis. What testing do you recommend prior to menarche to help prevent potential complications from concomitant Mullerian disorders?
 - a. pelvic exam
 - b. Pelvic US

- c. CT of the pelvis
- d. MRI of the pelvis
- e. No further screening

7. Your patient is a 10 year old girl who is found to have an obstructive Mullerian Anomaly. Her parents ask what treatment you recommend. You say:

- a. Ibuprofen and Oral Contraception Pills
- b. Tylenol
- c. Serial screening with ultrasound
- d. Surgical correction of the obstruction
- e. No intervention