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RESPONSE TO REVIEWERS

CHALLENGES IN PAEDIATRIC UROLOGY PRACTICE: A LIFELONG VIEW

WJUR-D-19-01106

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CHALLENGES IN PAEDIATRIC UROLOGIC PRACTICE: A LIFELONG VIEW

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STANDARDISATION OF DISEASE CLASSIFICATION
Standardised classification of congenital urologic conditions can improve management by creating consistent patient care and simplifying communication between care providers.
Neuropathic bladder dysfunction (NBD)

Neuromuscular dysfunction of the lower urinary tract can be congenital or acquired. The most common cause is neural tube defect of the spinal cord (spina bifida [SB]). SB is typically subclassified by anatomic type and level of the vertebral defect. Congenital NBD can also be due to sacral agenesis and anorectal malformations. Acquired aetiologies include pelvic surgery or radiation, central nervous system disease, and spinal cord insults.

NBD can affect storage and/or elimination of urine. Bladder storage may be altered by decreased detrusor compliance, reduced bladder capacity, detrusor overactivity or weak outlet. Emptying may be impaired by detrusor underactivity or detrusor sphincter dyssynergia (DSD). Urodynamic evaluation of the LUT can be non-invasive (bladder diaries, voiding observations and uroflowmetry) or invasive (urodynamic studies (UDS) with cystometry).[1] UDS should be performed when symptoms and/or non-invasive studies raise suspicion for NBD, obstruction, genitourinary anomalies, or significant vesicoureteral reflux (VUR) of unknown cause. In congenital NBD, UDS are recommended early in life to provide baseline assessment to identify those with a “hostile” bladder. Regular follow-up UDS can detect deterioration in bladder function.

Lower Urinary Tract Obstruction

The most common cause of pediatric bladder outlet obstruction in males is posterior urethral valves (PUV). Young[2] first classified PUV by anatomic type: type 1 (most common [>90%] with two leaflets descending from the verumontanum), type 2 (a normal anatomic variant no longer
considered pathologic), and type 3 (an obstructing ring with a small central opening). Dewan et al. hypothesized that most congenital posterior urethral obstructions were anatomically similar and should be called *congenital obstructing posterior urethral membrane* (COPUM).[3]

Prune-belly syndrome (PBS) consists of a triad of deficient abdominal wall musculature, bilateral intra-abdominal testicles and urinary tract dilation.[4] Woodard developed three categories of neonatal presentation:[5] Category I involves severe obstructive uropathy with renal dysplasia and oligohydramnions, resulting in pulmonary hypoplasia, Potter features, and usually neonatal demise. Category II has all features of the triad with less severe renal dysplasia. Category III is associated with incomplete or mild features of the triad without pulmonary hypoplasia or renal dysplasia.

**Bladder Exstrophy-Epispladias Complex (BEEC)**

BEEC presents along a spectrum from primary epispadias through classic bladder extrophy (BE) to cloacal extrophy (CE). **BE** involves malformations of the anterior abdominal wall, bladder, urethra, genitalia, and pelvic bones, believed to result from premature rupture of the cloacal membrane. Genital anomalies in **BE** can present with marked deficiency of penile corporal tissue, creating a short penis or shortened/stenotic vagina. The upper urinary tract is usually normal at birth, but incompetent ureteral orifices may result in VUR after bladder closure.

**CE**, also known as OEIS (omphalocele, extrophy, imperforate anus and spinal defects), typically includes neurospinal defects, hindgut deficiency, and omphalocele.[6] **CE** patients have complete phallic/clitoral separation, an even wider pubic diastasis, and gastrointestinal tract anomalies, typically with imperforate anus and shortened hindgut with caecum located between the
exstrophied hemi-bladders. In females, the Mullerian ductal structures are completely separated. Renal anomalies, such as renal agenesis and ectopia, are also more common.

BEEC may also be divided into typical (epispadias, BE and CE) and atypical (duplicated exstrophy, covered exstrophy and pseudoexstrophy) forms. Pseudoexstrophy describes the musculoskeletal defect associated with BE without urinary tract anomalies.[7] Superior vesical fissure presents with the same musculoskeletal defects but with a congenital vesicocutaneous fistula. Covered exstrophy is similar to BE, but the cloacal membrane persists.[8]

**Cloaca/anorectal malformations**

Persistent cloacal and anorectal malformations (ARM) range from mild anal anomalies to complex cloacal malformations. Many classification systems for ARM exist. The Wingspread classification was used to distinguish low, intermediate, and high ARM based on the levator ani muscle.[9] As surgeons embraced the posterior sagittal surgical approach to ARM, it was recognized that the fistula location had significant impact on long term outcomes, leading to the Pena classification.[10] The Krickenbeck classification was introduced to allow better comparison of follow-up with 3 categories: diagnostic (fistula site and degree of rectal/anal stenosis), surgical procedure performed, and functional outcome (degrees of incontinence and constipation).[11]

**Differences in sexual development**

Differences in sexual development (DSD) include a broad spectrum of endocrinopathies and structural anomalies that may lead to ambiguous genitalia. Multiple classification schema have
been used, but the 2008 Chicago Consensus introduced terminology to overcome dissatisfaction with older nomenclature.[12] Primary classification involves sex chromosome anomalies, XX, and XY disorders with the latter two subdivided into disorders of gonadal development, disorders of sex steroidogenesis, or other.

**Urethral anomalies**

The most common congenital anomaly of the penis is hypospadias. Duckett classified hypospadias by meatal position after correction of chordee: anterior (glanular, sub-coronal, distal penile), middle (midshaft) or posterior (proximal penile, penoscrotal, scrotal or perineal).[13] However, due to the variability of penile malformation in hypospadias, other parameters (chordee, penoscrotal transposition, urethral dysplasia, and preputial anomalies) impact surgical outcomes.[14, 15] Other hypospadias classifications (GMS and GUMS) have been proposed to include characteristics of the glans, urethral plate, meatal position, and penile shaft.[16] The HOPE, PPPS, HOSE and Hadidi scores additionally include assessment of postoperative outcomes and cosmetic appearance.[17]

Epispadias may present in isolation or, more commonly, as part of the BEEC complex. The urethra is found on the dorsum of the penis and is often associated with dorsal chordee and decreased anterior corporal length. **Unlike hypospadias, isolated epispadias without BE is often associated with deficient bladder neck development and impaired continence.** Classification in males is typically based on meatal location (glanular, penile, and penopubic).[6] Davis described 3 degrees of female epispadias: mild (patulous meatus), intermediate (urethra open dorsally along most of its length), and severe (involving the entire urethra and sphincter).[18]
Summary recommendation

Classification schema of congenital urological anomalies have been standardized based on anatomy, surgical considerations, and functional outcomes. It is recommended that best efforts be made to classify and document patient characteristics at birth and at routine follow-up. Ideally, classification systems should be highly reproducible and have low inter-user variability. (Level C)

NEUROPATHIC BLADDER AND LOWER URINARY TRACT OBSTRUCTION

Neuropathic bladder

Urinary sequeala of NBD include incontinence, urinary tract infections (UTI), urolithiasis, VUR, and renal deterioration.[19] Renal damage may occur in up to 60-80% of children in a few years without proper treatment, resulting in scarring and renal failure. The primary role of the urologist is to closely surveille bladder function in order to prevent upper tract damage.[20-22]

Routine follow-up is critical as bladder dysfunction can change during rapid growth in the first years of life and later during puberty. A large series found that 95% of myelomeningocele patients over age 4 years had NBD versus 65.1% of those with non-myelomeningocele forms of SB.[23] One analysis found that 37% (8-85%) of young adult meningomyelocele patients reported continence, 25% had some degree of chronic kidney disease (CKD), and 1.3% had end-stage renal disease (ESRD).[24]

Posterior urethral valves
The impact of the PUV on bladder and renal function is variable.[3, 25, 26] Poor urine concentrating ability is common and results in higher urine output which can negatively influence bladder physiology. Renal function must be closely monitored as up to 32% and 20% will develop CKD and ESRD, respectively.[27] Risk of development of ESRD is well described in periadolescence and adulthood.

Prune-belly Syndrome (PBS)
Similarly, patients with PBS have varying degrees of bladder and renal dysfunction and must be regularly assessed.

BLADDER PHYSIOLOGY

Neuropathic bladder
The degree and type of resulting LUT dysfunction cannot be accurately predicted by the level of the neuropathic lesion and may evolve with growth.[19] The largest known SB registry found only 45.8% of adults were continent with most (76.8%) performing clean intermittent catheterization (CIC).[28]

Posterior urethral valves
Bladder dysfunction often results from obstructive uropathy during fetal development despite early postnatal PUV ablation.[29] Boys with PUV may experience progressive storage and voiding symptoms as they age.[30-33] Up to 80% of affected infants have a small thick-walled and/or overactive bladder. Detrusor overactivity often resolves as bladder capacity increases.[30, 33, 34] Elevated postvoid residual (PVR) urine volume is common and often increases during puberty.
with increased outlet resistance secondary to prostatic development.[34] The detrusor can become underactive and occurs in approximately 1/3 of patients aged 4-7 years, 2/3 at puberty, and 83% after puberty.[30, 35, 36] A cycle of polyuria due to reduced renal urinary concentration, impaired bladder sensation, and high PVR can result in chronic bladder overdistension with urinary retention and secondary UTI.[37] Reflux into dilated upper tracts may also contribute to the elevated PVR as a result of secondary bladder filling.[38, 39] Not surprisingly, boys with a history of PUV often experience delayed achievement of urinary continence.

Prune Belly Syndrome

Unlike patients with PUV or NBD, the dilated urinary tract in PBS is usually a low-pressure system with favorable detrusor compliance and rare overactivity. PVR are typically high secondary to detrusor underactivity and VUR (found in up to 75%) into dilated upper tracts.[40, 41]

Lifelong follow-up is mandatory for all with congenital bladder dysfunction, as detrusor and the sphincter function can change over time, often with silent and potentially preventable renal insult. (Grade C)

TREATMENT AND OUTCOME

The primary goals of management are preservation of renal function and prevention of UTIs with later attainment of urinary continence in most.

Neuropathic bladder
With the vast majority of adolescent and adult SB patients performing CIC,[28] institution of CIC early in childhood may be prudent. There is controversy whether early initiation of CIC soon after birth results in better renal outcomes and a decreased need for bladder augmentation.[38, 39, 42] Anticholinergic medications are frequently used to treat detrusor overactivity and reduced detrusor compliance [43, 44] with approximately half of adults with SB taking them.[28] Mirabegron, a β3 agonist, may be used, but experience in NBD is limited.[45, 46]

For bladders refractory to anticholinergics, intradetrusor injection of onabotulinumtoxin A is a non-surgical option.[47, 48] The effectiveness is better in bladders with detrusor overactivity compared to those with poor compliance.[49, 50] Neuromodulation, including intravesical electrical stimulation of the bladder,[51] sacral nerve stimulation,[52] transcutaneous neuromodulation,[53] and intradural somatic-to-autonomic nerve anastomosis[54, 55] have been reported in patients with SB but has to be considered experimental at this time. There are limited reports of urethral dilatation to improve bladder characteristics in highly selected patients.[56] Vesicostomy can be useful in medically-refractory infants and young children, if the parents will not or cannot perform CIC.[57] In older patients who fail the above therapies, bladder augmentation or urinary diversion is an option.[58, 59] Augmentation cystoplasty is effective in increasing bladder capacity and lowering storage pressure as well as improving urinary continence.[60, 61] In rare situations with a unilateral non-functioning kidney with a dilated ureter, ureterocystoplasty can be performed.[62, 63] Use of tissue-engineered autologous bladder tissue to avoid the complications associated with bowel interposition in enterocystoplasty remain experimental.[64, 65]
Continent cutaneous catheterizable channels (Mitrofanoff or Yang-Monti) are commonly created for patients who are unable to perform CIC per urethra. Though highly effective, the revision rate in long-term studies can be as high as 50-60%. [66, 67]

In patients with sphincter incompetence, pharmacologic therapy with α-adrenergic receptor agonists is rarely effective. [68] Surgical intervention is typically the only solution. [69-71] Synthetic slings in girls with NBD have had poor track record and should not be used. [72] Artificial urinary sphincters (AUS) may obtain superior continence rates in up to 85% in well-selected patients and is the only surgical option that can preserve the ability to void spontaneously. [73] Due to its size, AUS is typically reserved for post-pubertal patients with good manual dexterity. CIC through a urethra with an AUS is possible with proper patient selection. [74] However, these devices have the risk of cuff erosion or device infection as well as the mechanical failure/fluid leak; in a series of 32 children with mean follow up of 15 years, 41% had the device removed, and the remaining 19 patients underwent 34 revision surgeries. [75] Bladder neck reconstruction in NBD is less successful than in bladder exstrophy. [76] After a failed bladder outlet procedure, bladder neck closure with a continent catheterizable stoma may be considered but should be considered as the option of last resort. Complications occur in one-third and include fistulae in up to 15% and an increased risk of bladder stones, bladder perforation and upper tract deterioration. [77, 78] In those who will not or cannot perform CIC, an incontinent urinary diversion (cutaneous vesicostomy or intestinal conduit) may be required.

Posterior urethral valves
Renal function often improves slightly in the first three years of life and is typically stable from age 3 to puberty. Following the onset of puberty, up to 50% will develop renal failure. Nadir serum creatinine <0.7 mg/dL in the first year of life and increasing proteinuria can be predictive of later need for renal replacement therapy. [79]

Valve bladder (voiding dysfunction commonly encountered in PUV) has been well-described.[80, 81] Bladder functional outcomes in adult life have not been addressed well.[81-84] In boys with detrusor overactivity, anticholinergic medications may be beneficial,[83, 85] but with a low risk of reversible myogenic failure and worsening retention.[85, 86] Bladder emptying can be improved by timed and double voiding.[36, 87] α-blockers, such as terazosin and tamsulosin, may be helpful in boys with elevated PVR or straining to void.[88, 89] CIC may be necessary in those with high daytime PVR;[82, 90, 91] however, unlike NBD, boys with PUV typically have normal urethral sensation. In such cases, adequate bladder emptying may only be possible with a continent catheterizable channel.[82, 92] Some may require overnight catheter drainage in the setting of obligatory nocturnal polyuria.[37, 93]

Rarely, bladder augmentation may be required to manage valve bladders with reduced capacity and/or compliance.[94, 95] The need for augmentation prior to renal transplantation is controversial as the new kidney will often end the polyuria caused by the poor concentrating ability of the native kidneys, and bladder dynamics will subsequently improve.[96] Following transplantation, graft function needs to be closely monitored to be sure that the valve bladder dysfunction and compliance issues do not harm the kidney.[97]
Prune Belly Syndrome

Prior management with near universal surgical reconstruction to attempt to normalize urinary tract anatomy has evolved to one that is much less surgical. Double and timed voiding after toilet training has fewer complications than early total urinary reconstruction.[98, 99] CIC is an option in those with poor emptying – either per urethra or surgically created channel.[41, 100]. If the upper urinary tract deteriorates, surgical correction of VUR or massive ureteral dilation may be considered; however, complication rates are significant with post-operative ureteral obstruction in up to 40% and persistent VUR in 30% [101]

Abdominal wall reconstruction is also controversial.[101] Arguments for reconstruction include improvement of the abdominal muscular tone, improved bladder sensation, better efficiency of bladder emptying, and improved cosmesis.[102-104] Conversely, some boys do well with a non-surgical approach with a corset.[105, 106]

FOLLOW-UP SCHEDULE

Neuropathic bladder

EAU/ESPU guidelines recommend proactive treatment with CIC +/- anticholinergic medication starting in the first months of life.[107]

Lifelong follow-up is required with regular examination, renal bladder ultrasound, renal function monitoring by serum creatinine and/or cystatin C, blood pressure and urinalysis for proteinuria. The need for regular urodynamic assessment in patients without changes in upper tracts, continence or UTI frequency is not well-delineated.[107] Following augmentation cystoplasty,
monitoring for metabolic acidosis and serum vitamin B₁₂ deficiency and imaging to detect urolithiasis are also recommended. Routine cystoscopy for malignancy screening after augmentation is not effective. [108, 109] but cystoscopy should be performed in the setting of gross hematuria or recurrent UTI. (Grade C)

**Posterior urethral valves and prune belly syndrome**

Annual urologic follow-up is required for these boys through puberty with longer follow-up dependent on urinary symptoms and the degree of CKD. Evaluation should include examination, serum creatinine, determination of bladder function (by sonography or uroflow studies), and upper tract imaging. Urodynamics should be reserved for worsening incontinence, increasing frequency of UTIs, new hydronephrosis, or worsening GFR. In cases with bladder augmentation or continent catheterizable channel, the follow-up is similar to those with NBD. (Grade C)

**BLADDER EXSTROPHY-EPISPADIAS COMPLEX**

The techniques for management of BE have evolved tremendously since the first described neonatal bladder closure in 1885. The three primary approaches employed in the 21st century are: the modern staged repair,[110] the complete primary repair,[111] and the Kelly repair.[112] Undoubtedly, children with BEEC undergo a number of subsequent reconstructive operations and often require further reconstruction in adulthood.[113]

The modern staged repair of BE begins with neonatal closure of the bladder, posterior urethra, abdominal wall and bony pelvis.[114] Closure may be delayed if the bladder template is too small or rigid to allow spherical closure.[115] The second stage in boys to correct the epispadias usually
occurs at 6-12 months of age. The next step to correct VUR and attain continence by bladder neck reconstruction is typically performed usually at least 5 years of age.

Complete primary repair of extrophy combines bladder closure with epispadias repair and bladder neck reconstruction in a single procedure.[111, 116] Over the past few years, some are moving to delaying primary repair when the child beyond the newborn period.

The Kelly technique is a staged approach with neonatal closure of the bladder dome and inguinal hernia repair without osteotomies.[112, 117] The second stage at 3-6 months of age involves radical mobilization of soft tissue, including the pelvic floor muscles, to create the sphincteric complex with simultaneous proximal urethra closure. In males, penile lengthening occurs at this stage, and the urethra is left at the penoscrotal junction. Advancement of the urethral meatus to the glans is performed around three years of age.

**Evaluation and Follow-up**

Long term BEEC management focuses on preservation of renal function, attainment of urinary continence, and genital reconstruction for satisfactory sexual function. Renal function is paramount but can be compromised by urinary tract reconstruction; fortunately, the rates of CKD have decreased with refinements in surgical techniques.[118] A full understanding of the closure technique utilized are important, and surgical records should be obtained if not known. No set guidelines exist, but most recommend annual renal/bladder ultrasound and serum creatinine.
Worsening renal function may result from recurrent UTI, ureteral or urethral obstruction, VUR (primary or secondary) or high bladder storage pressures.[118]

Urinary continence has a substantial impact upon quality of life and should be regularly assessed. Social continence is typically defined as the ability to stay dry for 3 hours.[110, 113, 119] Most patients require some type of bladder neck procedure to create adequate outlet resistance while allowing voiding per urethra. Those that are unable to adequately empty their bladders by voiding may require CIC to achieve dryness. Catheterization through the reconstructed urethra may not be possible for all, and a continent catheterizable channel may be required. For some, continence may only be achieved by bladder neck closure.

Surveillance for tumor formation later in life is particularly an issue for BEEC patients.[120] In the adult extrophy population alone, it has been demonstrated that the risk of malignancy is 17.5%, 700 times greater than the healthy population, independent of the bladder reconstruction status.[121, 122] Transitional cell, adenocarcinoma and squamous cell bladder cancers have all occurred in extrophy bladders. Evolving reconstructive techniques and better counseling for carcinogen avoidance (e.g., tobacco) may reduce risk in the future. [120] Surveillance for bladder tumors is complicated in this population given their reconstructed urethras are often of small caliber and make cystoscopy +/- biopsy difficult in adult life.

Genital issues in both males and females with BEEC arise in adolescence. The penis is shorter and wider in BEEC often requiring lengthening procedures to allow intercourse.[123, 124] Some
males will require secondary genitoplasty for penile lengthening;[125] whereas, neophallus creation may be necessary in the most severe cases.[126] Vaginal stenosis is common with many females needing surgery to allow tampon use and to engage in intercourse.[127] Incontinence and concerns about genital appearance and function can amplify the pre-existing anxiety problems common to many children with chronic medical problems, and counselling by sexual therapists and mental health professionals should be encouraged.[128]

Complications and issues into adulthood

Stones are common in patients with bowel used in urinary reconstruction as mucus can be a nidus for mineral precipitation.[129] Retained sutures in the urinary tract can be another nidus for stone formation in this population and must be addressed surgically. Patients should be counseled to stay well-hydrated and perform regular generous bladder irrigation to remove mucus. Regular monitoring with renal bladder ultrasound is recommended for stone detection. If stones do occur, access to the bladder and ureters may be compromised by prior surgical reconstruction, and percutaneous approaches may be required.

Evaluation of incontinence can be complicated in BEEC patients. Typically, the patient must be compliant with a strict bladder emptying regimen, as well as additional measures such as double voiding or CIC. Imaging may help demonstrate adequate emptying after bladder neck reconstruction. Patients reporting changes in continence or shortening of their dry intervals could also be experiencing worsening detrusor compliance. Urodynamic evaluation must be available, and those with poor capacity and/or detrusor compliance may need anticholinergic medication,
intradetrusor botulinumtoxin injection, or bladder augmentation. Rather unique to BEEC patients, incontinence can also result from vesicocutaneous or urethrocutaneous fistulae which require closure and coverage with a muscle flap.[130, 131]

Sexual function and fertility are complex in the BE population. Vaginal stenosis may complicate intercourse, conception and delivery.[132, 133] Males usually have normal spermatogenesis but may require assisted reproductive technology, due to retrograde ejaculation or iatrogenic ejaculatory duct obstruction.[132, 134, 135] CE patients present even greater challenges. Males may be have neurogenic erectile and ejaculatory dysfunction,[136] and females typically have a high incidence of Müllerian anomalies with duplicated vagina and uterus as well as separated mons, labia, and clitoris.[137]

**SUMMARY RECOMMENDATIONS**

*A multidisciplinary approach to the management of children and adolescents with BEEC is critical as they move towards adulthood to ensure the preservation of renal function and to optimize quality of life. As adults, these patients require care by urologists with sub-specialty experience. For females, conception and delivery may require genetic specialists, reconstructive gynecologists/urologists, infertility specialists, and high-risk obstetricians, along with shared urologic care during pregnancy and delivery. (Level C)*
GENITOURINARY ANOMALIES AFFECTING THE FEMALE REPRODUCTIVE SYSTEM

In the absence of Müllerian inhibiting substance (MIS), the Müllerian ducts fuse and develop into the uterus, fallopian tube, and upper vagina. Their proximity to the Wolffian ducts are believed to be responsible for the common association of Müllerian duct anomalies with ureteral/renal anomalies.[138] The vaginal plate is formed as the caudal end of the ducts contact the urogenital sinus and promote proliferation of the sinovaginal bulbs. Without androgens, the external genitalia become distinctly female as the genital tubercle elongates into the clitoris, the urogenital folds develop into the labia minora, and the labioscrotal swellings become the labia majora.

Müllerian anomalies are relatively common, affecting approximately 5.5% of females. [139] They can result from abnormalities of Müllerian duct development (vaginal atresia, absence of uterus), fusion (didelphys, septate) or migration (persistent urogenital sinus.) Transverse vaginal septum results from failure of vertical vaginal fusion and can be occur at any level, but most commonly in the upper 1/3 of the vagina. Classification is by distance from the hymen: low (< 3 cm), mid (3-6 cm), and high (> 6 cm). Septa typically present during adolescence with progressive episodic abdomino-pelvic pain and primary amenorrhea due to obstructed menstruation.[140] Obstructed Hemi-vagina Ipsilateral Renal Agenesis (OHVIRA) is defined by uterine didelphys, obstructed hemi-vagina and ipsilateral renal agenesis (from failed ipsilateral Wolffian duct development.) With this anomaly, adolescents can present with regular or irregular periods as well as episodic abdomino-pelvic pain.[141] Mayer Rokitansky Kuster Hauser Syndrome (MRKH) is defined by the absence of a normal uterus and vagina in a 46,XX
female and is caused by inadequate Müllerian development. Affected girls typically present with primary amenorrhea; examination reveals a shallow vaginal pouch with normal secondary sex characteristics. Associated urinary tract anomalies occur in 30-40% of cases.[142]

Congenital adrenal hyperplasia (CAH) results from autosomal recessive endocrinopathies of adrenal cortisol synthesis. 21-hydroxylase deficiency is the most common, accounting for up to 90% of cases.[143] The classic form is simply virilizing with normal aldosterone biosynthesis; whereas, the salt-wasting form involves impaired aldosterone production. Virilization can begin in the seven week of gestation as the 46,XX fetus from exposure to systemic adrenal androgens and can result in “ambiguous genitalia” with an enlarged clitoris, rugated and fused labia majora, and common urogenital sinus. The Prader scale classifies the variable presentation from stage 1 (phenotypic female with mild clitoromegaly) to stage 5 (phenotypic male). The length of the common urogenital sinus from the vagina-urethral junction to the external meatus is also dependent on the degree of virilization. Without testicular MIS, the uterus, upper vagina, and fallopian tubes form normally, so fertility is usually preserved. This differentiates CAH from other types of DSD, many of which have no reproductive potential.

*It should be noted that reconstructive surgery was previously performed in infancy and childhood, but changing social paradigms related to gender assignment and surgery in more recent years has resulted in characterization of these anomalies in childhood, but often deferred surgical reconstruction until the patient is able to participate in surgical decision-making. The impact of this paradigm shift on cosmetic, functional, and*
psychologic outcomes for patients affected by conditions that result in ambiguous genitalia will not be borne out for decades.[144]

SUMMARY RECOMMENDATIONS

*Mullerian anomalies may be noted at birth or can present at puberty or early adult life.*

*Experienced gynecological management is critical to achieving successful cosmetic and functional outcomes. Co-management with urologists is required when the urinary tract is also involved. A multidisciplinary team, including psychologists and endocrinologists, contribute to improved physical and mental health outcomes. (Grade C)*

FOLLOW-UP OF HYPOSPADIAS IN CHILDHOOD AND ADOLESCENCE

The goals of hypospadias management remain constant with age: 1) satisfactory urinary stream; 2) a sufficient straight penis with a distal meatus to allow satisfactory sexual function and fertility, and 3) satisfactory penile appearance.

No guidelines exist regarding optimal follow-up following hypospadias repair. 70-90% of cases are distal,[145] and surgical outcomes are typically good for distal cases. Thus, universal prolonged follow-up throughout childhood may be unnecessary after repair of uncomplicated distal hypospadias. Self-esteem may be affected by repeated urologist visits with little chance of
detecting complications affecting urinary or sexual function. At least 80% of complications occur in the first year following hypospadias repair, and it has been estimated that prolonged follow-up would needed in 14 boys to detect each complication.[146] Over 70% of urethrocutaneous fistulae, the most common complication, are diagnosed within the first year after surgery.[147] Delayed fistulas are typically small and have obvious symptoms, further limiting the utility of universal prolonged follow-up. More complicated distal cases and most proximal cases have much higher risks of complications in both short term and long term. Long and Canning [144] noted an overall complication of 17% in a ten year series of hypospadias repairs, but the rate was 45% for the proximal cases.[148] Therefore, re-evaluation in adolescence is recommended due to the relatively higher risks of functional and psychological suboptimal results.[149]

Urethral obstruction is a more worrisome complication. Calibration of the neo-urethra in the clinic should be reserved for infants with obstructive voiding symptoms and/or small meatus, and it should be performed under sedation or anesthesia in older boys.[150] Uroflowmetry can be useful in symptomatic toilet trained boys but is likely not routinely indicated. Because flow rates usually improve at puberty, watchful watching is encouraged for most boys with obstructive symptoms.[151, 152]

In terms of sexual function, adolescent boys with history of proximal hypospadias repair have similar age for sexual debut and rates of sexual activity as normal controls and those with history of distal hypospadias repair, with few reporting erectile and ejaculatory dysfunction.[153] Proximal hypospadias is associated with greater concerns about penile length as well as lower
scores for orgasmic and ejaculatory function, but not erectile function.[154] Penile perception scores also show decreased satisfaction among those with more proximal hypospadias..[155]

Recommendation:

Following successful distal hypospadias repair, routine follow-up can likely be stopped 6-12 months post-operatively, but parents should be counselled regarding obstructive voiding symptoms or a second or abnormal stream. There is a greater risk of complications and associated psychologic concern after proximal hypospadias repair, so continued follow up during childhood and through puberty is reasonable. (Grade B)
Authors’ Contributions

Wiener – Project development; manuscript writing

Huck - manuscript writing

Blais - manuscript writing

Rickard - manuscript writing

Lorenzo - manuscript writing

Di Carlo - manuscript writing

Mueller - manuscript writing

Stein - manuscript writing

Conflict of Interest: The authors declare that they have no conflict of interest.

Statement of human rights
This is a review that contains no original research. We assume that the referenced studies were approved by the appropriate institutional and/or national research ethics committee and were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent: This is a review that contains no original research. We assume that the referenced studies were performed with informed consent obtained from all individual participants included in the studies.
References:


