CONGENITAL ANOMALIES IN CHILDREN

EDITORS: Catherine R. deVries, MD Rien Nijman, MD



Vancouver, Canada, September 8-12, 2013









A Joint SIU-ICUD International Consultation

Vancouver, Canada, September 8-12, 2013

Co-sponsored by SIU (Société Internationale d'Urologie) ICUD (International Consultation on Urological Diseases)





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Abbreviations Used in the Text

AMH	anti-Müllerian hormone
AR	androgen receptor
ARM	anorectal malformations
ASTRA	anterior sagittal transrectal approach
AUS	artificial urinary sphincter
BE	bladder exstrophy
BMI	body mass index
САН	congenital adrenal hyperplasia
CAIS	complete androgen insensitivity syndrome
CDUS	colour Doppler ultrasonography
CE	cloacal exstrophy
CGRP	calcitonin gene-related peptide
CIC	clean intermittent catheterization
CIS	carcinoma in situ
CPRE	complete primary repair of exstrophy
СТ	computed tomography
DHT	dehydrotestosterone
DMSA	dimercaptosuccinic acid
DNA	deoxyribonucleic acid
DSD	disorders of sexual development
EMS	external masculinization score
ER	estrogen receptor
FS	Fowler-Stephens
FSH	follicle-stimulating hormone
GB	gonadoblastoma
GBY	gonadoblastoma locus on Y
GCT	germ cell tumors
GOR	grade of recommendation
HCG	human chorionic gonadotropin

HSD	hydroxysteroid dehydrogenase
ICUD	International Consultation on Urological Diseases
lief	international index of erectile function
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
LNSV	lymphatic non-sparing laparoscopic varicocelectomy
LOE	level of evidence
LSV	lymphatic-sparing laparoscopic varicocelectomy
MACE	Malone antegrade continence enema
MGD	mixed gonadal dysgenesis
MOS	medical outcomes study
MPFF	micronized purified flavonoid fraction
MRI	magnetic resonance imaging
MRKHS	Mayer-Rokitansky-Küster-Hauser syndrome
NS	not significant
ОН	hydroxylase
OHD	hydroxylase deficiency
OMG	oral mucosa–free grafts
PAIS	partial androgen insensitivity
PGD	prostaglandin
POSNA	Pediatric Orthopedic Society of North America
PSARVUP	posterior sagittal anorecto-vaginourethroplasty
PUM	partial urogenital mobilization
PV	pediatric varicocele
RALV	robotic-assisted laparoscopic varicocelectomy
RCT	randomized, controlled trial
RSTM	radical soft tissue mobilization
SCF	stem cell factor
SD	standard deviation
SRY	sex-determining region Y
TIP	tubularized incised urethral plate
TSPY	testis-specific protein on Y
TUM	total urogenital mobilization

UDT	undescended testis
UGS	urogenital sinus
US	ultrasound
USO	ureterosigmoidostomy
UTI	urinary tract infection



Preface



Catherine R. deVries, MD



Rien Nijman, MD

Congenital anomalies of the urinary tract and genitalia are common worldwide. They have the potential to greatly impact the quality of life of children and, if uncorrected, of adults as well. While pediatric urology training fellowships are available in the United States and in Europe, they are not common in other parts of the world. In Sub-Saharan Africa, there is not a single pediatric urology subspecialty training program at the time of this writing. Training in general programs often does not cover management of genital anomalies, and the literature can be difficult to access for surgeons in low- and middle-income countries.

Surgeons caring for children born with genital anomalies have become more and more aware of the need to increase their knowledge of and improve their skills to treat these anomalies. Annual scientific meetings are now organized not only in Europe and the United States, but also in the far East, Asia, South America, and Australia. Yet, the literature and analysis of it can be inaccessible or confusing to those who need it most, because it is often not distilled or analysed for quality of evidence.

Although worldwide there have been regional approaches and traditions to the surgical care of genital anomalies, with globalization and improved communications, we are now able to share data and outcomes, to work together at the operating room table and via telemedicine. We can now share experiences in a collaborative manner, in real time.

This international consultation on genital anomalies brings together experts from around the world to review the evidence for disease etiology and management. It does not intend to be an exhaustive or definitive work, nor is it a textbook. Rather, it is a review of the global literature on anomalies of the genitalia and lower urinary tract, with an emphasis on evidence. Where possible, recommendations are made, based on that evidence. During the preparation of this ICUD, it was noted by many of the contributing authors that long-term outcome data are lacking. This probably is the biggest challenge for all of us: to provide information on long-term outcome. Most of the children are very young when they undergo a surgical correction with the best intentions, but what we believe to be "best practice" may in the long-term not turn out to be such a good treatment. Because treatment modalities improve and strategies may change, we must be mindful to evaluate outcome when these children reach adolescence and adulthood. In the interest of our patients, we should combine our data and provide better guidelines for future generations.

This consultation is divided into 9 chapters: Embryology of the External Genitalia; Cryptorchidism, Hernia and Hydrocele; Hypospadias; Disorders of Sex Development; Classic Exstrophy; Cloacal Exstrophy; Cloacal and Urogenital Sinus Anomalies; Pediatric Varicocele, Micropenis, and other Anomalies; and Adolescent Urology. Each chapter was a team effort, with a chair coordinating the final output. A steering committee included the editors and reviewers, and the ICUD coordinating committee.

We are grateful to Drs. Raimund Stein and Marc Cendron for assisting in chapter review and to Dr. Paul Abrams for coordination of the ICUD process. And finally, the Societé Internationale d'Urologie has supported this ICUD with editing, web and print publishing, a symposium, and work sessions at the SIU annual meeting in 2013 and with financial support.

We thank all our colleagues who have generously contributed their time and expertise to this consultation, which will benefit not only pediatric urologists, but all who care for children with genital anomalies—and most of all, our patients born with genital anomalies.

Catherine R. deVries, M.D. Rien Nijman, M.D.

Evidence-Based Medicine Overview of the Main Steps for Developing and Grading Guideline Recommendations

P. Abrams, S. Khoury, A. Grant

Introduction

The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organisation (WHO). In the last ten years, consultations have been organized on BPH, prostate cancer, urinary stone disease, nosocomial infections, erectile dysfunction and urinary incontinence. These consultations have looked at published evidence and produced recommendations at four levels: highly recommended, recommended, optional and not recommended. This method has been useful but the ICUD believes that there should be more explicit statements of the levels of evidence that generate the subsequent grades of recommendations.

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence-Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001, www.cebm.net).

The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the consultations organized by ICUD. It is highly desirable that the recommendations made by the consultations follow an accepted grading system supported by explicit levels of evidence.

The ICUD proposes that future consultations should use a modified version of the Oxford system which can be directly "mapped" onto the Oxford system.

1. First Step

Define the specific questions or statements that the recommendations are supposed to address.

2. Second Step

Analyze and rate (level of evidence) the relevant papers published in the literature.

The analysis of the literature is an important step in preparing recommendations and their guarantee of quality.

2.1 What papers should be included in the analysis?

- Papers published, or accepted for publication in the peer-reviewed issues of journals.
- The committee should do its best to search for papers accepted for publication by the peer-reviewed journals in the relevant field but not yet published.
- Abstracts published in peer-reviewed journals should be identified. If of sufficient interest, the author(s) should be asked for full details of methodology and results. The relevant committee members can then "peer review" the data, and if the data confirms the details in the abstract, then that abstract may be included, with an explanatory footnote. This is a complex issue – it may actually increase publication bias as "uninteresting" abstracts commonly do not progress to full publication.
- Papers published in non-peer-reviewed supplements will not be included. An exhaustive list should be obtained through:
 - The major databases covering the last ten years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index).
 - II. The table of contents of the major journals of urology and other relevant journals, for the last three months, to take into account the possible delay in the indexation of the published papers in the databases.

It is expected that the highly experienced and expert committee members provide additional assurance that no important study would be missed using this review process.

2.2 How are papers analyzed?

Papers published in peer-reviewed journals have differing quality and level of evidence. Each committee will rate the included papers according to levels of evidence (see below).

The level (strength) of evidence provided by an individual study depends on the ability of the study design to minimize the possibility of bias and to maximize attribution.

It is influenced by:

The type of study, whose hierarchy is outlined below:

- Systematic reviews and meta-analysis of randomized controlled trials
- Randomized controlled trials
- Non-randomized cohort studies

How well the study was designed and carried out

Failure to give due attention to key aspects of study methodology increases the risk of bias or confounding factors, and thus reduces the study's reliability.

The use of **standard checklists** is recommended to insure that all relevant aspects are considered and that a consistent approach is used in the methodological assessment of the evidence.

The objective of the checklist is to give a quality rating for individual studies.

How well the study was reported

The ICUD has adopted the CONSORT statement and its widely accepted checklist. The CONSORT statement and the checklist are available at www.consort-statement.org.

- Case-control studies
- Case series
- Expert opinion

2.3 How are papers rated?

Papers are rated following a level of evidence scale.

ICUD has modified the Oxford Centre for Evidence-Based Medicine levels of evidence.

The levels of evidence scales vary between types of studies (i.e. therapy, diagnosis, differential diagnosis/ symptom prevalence study) the Oxford Centre for Evidence-Based Medicine Website: www.cebm.net.

3. Third Step: Synthesis of the Evidence

After the selection of the papers and the rating of the level of evidence of each study, the next step is to compile a summary of the individual studies and the overall direction of the evidence in an **Evidence Table**.

4. Fourth Step: Considered Judgment (Integration of Individual Clinical Expertise)

Having completed a rigorous and objective synthesis of the evidence base, the committee must then make a judgment as to the grade of the recommendation on the basis of this evidence. This requires the exercise of judgment based on clinical experience as well as knowledge of the evidence and the methods used to generate it. Evidence-based medicine requires the integration of individual clinical expertise with the best available external clinical evidence from systematic research. Without the former, practice quickly becomes tyrannized by evidence, for even excellent external evidence may be inapplicable to, or inappropriate for, an individual patient. On the other hand, without current best evidence, practice quickly becomes out of date. Although it is not practical to lay our "rules" for exercising judgment, guideline development groups are asked to consider the evidence in terms of quantity, quality, and consistency, as well as applicability, generalizability and clinical impact.

5. Fifth Step: Final Grading

The grading of the recommendation is intended to strike an appropriate balance between incorporating the complexity of type and quality of the evidence, and maintaining clarity for guideline users.

The recommendations for grading follow the Oxford Centre for Evidence-Based Medicine. The levels of evidence shown below have again been modified in the light of previous consultations. There are now four levels of evidence instead of five.

The grades of recommendation have not been reduced and a "no recommendation possible" grade has been added.

6. Levels of Evidence and Grades of Recommendation for Therapeutic Interventions

All interventions should be judged by the body of evidence for their efficacy, tolerability, safety, clinical effectiveness and cost-effectiveness. It is accepted that, at present, little data exists on cost-effectiveness for most interventions.

6.1 Levels of evidence

Firstly, it should be stated that any level of evidence may be positive (the therapy works) or negative (the therapy doesn't work). A level of evidence is given to each individual study.

Level of Evidence	Criteria
I	 Incorporates Oxford 1a, 1b Usually involves: meta-analysis of trials (randomized controlled trials [RCTs]) or, a good-quality RCT or, "all or none" studies in which treatment is not an option (e.g. in vesicovaginal fistula)
II	 Incorporates Oxford 2a, 2b and 2c Includes: <i>Iow-quality RCT</i> (e.g. <80% follow-up), <i>meta-analysis</i> (with homogeneity) of <i>good-quality prospective cohort studies</i> May include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group
III	 Incorporates Oxford 3a, 3b and 4 Includes: good-quality retrospective case-control studies, where a group of patients who have a condition are matched appropriately (e.g. for age, sex, etc.) with control individuals who do not have the condition good-quality case series, where a complete group of patients, all with the same condition, disease or therapeutic intervention, are described without a comparison control group
IV	 Incorporates Oxford 4 Includes <i>expert opinion</i>, where the opinion is based not on evidence but on "first principles" (e.g. physiological or anatomical) or bench research. The <i>Delphi process</i> can be used to give expert opinion greater authority: involves a series of questions posed to a panel answers are collected into a series of "options" these "options" are serially ranked; if a 75% agreement is reached, then a Delphi consensus statement can be made

6.2 Grades of recommendation

The ICUD will use the four grades from the Oxford system. As with levels of evidence, the grades of evidence may apply either positively (procedure is recommended) or negatively (procedure is not recommended). Where there is disparity of evidence, for example if there were three well-conducted RCTs indicating that Drug A was superior to placebo, but one RCT whose results show no difference, then there has to be an individual judgment as to the grade of recommendation given and the rationale explained.

Grade A recommendation usually depends on consistent level I evidence and often means that the recommendation is effectively mandatory and placed within a clinical-care pathway. However, there will be occasions where excellent evidence (level I) does not lead to a Grade A recommendation, for example, if the therapy is prohibitively expensive, dangerous or unethical. Grade A recommendation can follow from Level II evidence. However, a Grade A recommendation needs a greater body of evidence if based on anything except Level I evidence.

Grade B recommendation usually depends on consistent level 2/3 studies, or "majority evidence" from RCTs.

- Grade C recommendation usually depends on level 4 studies or "majority evidence" from level 2/3 studies or Delphi processed expert opinion.
- **Grade D** "No recommendation possible" would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Delphi.

7. Levels of Evidence and Grades of Recommendation for Methods of Assessment and Investigation

From initial discussions with the Oxford group, it is clear that application of levels of evidence/grades of recommendation for diagnostic techniques is much more complex than for interventions. The ICUD recommends that, as a minimum, any test should be subjected to three questions:

- Does the test have good technical performance? For example, do three aliquots of the same urine sample give the same result when subjected to dipstick testing?
- 2. Does the test have good diagnostic performance, ideally against a "gold standard" measure?
- 3. Does the test have good therapeutic performance, that is, does the use of the test alter clinical management? Does the use of the test improve outcome?

For the third component (therapeutic performance) the same approach can be used as for section 6.

8. Levels of Evidence and Grades of Recommendation for Basic Science and Epidemiology Studies

The proposed ICUD system does not easily fit into these areas of science. Further research needs to be carried out in order to develop explicit levels of evidence that can lead to recommendations as to the soundness of data in these important aspects of medicine.

Conclusion

The ICUD believes that its consultations should follow the ICUD system of levels of evidence and grades of recommendation, where possible. This system can be mapped to the Oxford system.

There are aspects to the ICUD system that require further research and development, particularly diagnostic performance and cost-effectiveness, and also factors such as patient preference.

Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations

Levels of Evidence	Description
Ι	Meta-analysis of RCTs or high-quality RCT
II	Low-quality RCT or good-quality prospective cohort study
III	Good-quality retrospective case-control study or cohort study
IV	Expert opinion

Abbreviation: RCT=randomized controlled trial

Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations

Grades of Recommendation	Description
А	Usually consistent with level I evidence
В	Consistent level II or III evidence or "majority evidence" from RCTs
C	Level IV evidence or "majority evidence" from level II or III studies
D	No recommendation possible because of inadequate or conflicting evidence

RCT=randomized controlled trial

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1.1 **Development and Differentiation of the Genital Tubercle, Male Urethra, and Labioscrotal Swellings**

The human penile and clitoral genitalia develop from a common indistinguishable genital tubercle.¹ Sexual differentiation begins at 7 to 8 weeks of gestation. Under the influence of the sex-determining region Y (SRY) gene, the bipotential gonad differentiates into a testes, ultimately resulting in androgen production. External genital development undergoes two stages that can be distinguished by hormone-independent growth prior to testicular development and hormone-dependent growth under the influence of androgens.

Hormone-independent development occurs between conception and 7 to 8 weeks of gestation.¹ This is under the influence of a cascade of genes including sonic hedgehog, BMP4, Glia 123, and Wilms' tumour gene. The early development of the external genitalia is similar in both genders (**Figure 1-1**).

While the anorectal canal and urogenital sinus are being separated by the urorectal septum, the mesoderm anterior and cranial to the phallic segment of the urogenital sinus expands. This forms the genital tubercle, which will eventually form the phallic segment. In this indifferent stage, around the third week of development, mesenchyme cells originating in the region of the primitive streak migrate around the cloacal membrane to form a pair of cloacal folds (or urogenital folds). Cranial to the cloacal membrane, the folds unite to form the genital tubercle; whereas in the caudal part, cloacal folds are subdivided into the urethral folds anteriorly and to the anal folds posteriorly.



Simultaneously, another pair of genital swellings appears on each side of the urethral folds. These are called genital swellings or labioscrotal swellings, as they later form scrotal swellings in the male and labia majora in the female. The appearance of the external genitalia is similar in male and female embryos through the 12th week of gestation and it is impossible to distinguish between two sexes based on the external appearance.

At approximately 8 weeks of gestation, the external genitalia begin to differentiate secondary to the action of androgens, both testosterone and dihydrotestosterone. There is an induction of posterior fusion of the genital folds as well as growth of the genital tubercle into a normal phallic structure.

The penile urethra forms as a result of fusion of the two edges of the urethral folds, with subsequent remodeling into a tubular structure. Following the rupture of the cloacal membrane, much of the floor of the phallic segment of the urogenital sinus is lost, but the roof of the phallic segment remains and eventually expands along the lower surface of the genital tubercle as the genital tubercle enlarges. This endodermal extension forms the urethral plate (or urethral membrane) (**Figure 1-2**).

During the elongation of the phallus, urethral folds are pulled forward so that they will form the lateral walls of the urethral groove. Initially, the urethral groove and urethral folds extend only part of the way along the elongating phallus. In other words, the urethral groove extends along the caudal aspect of the elongated phallus, but it does not reach the distal part that will later be called the *glans*. The epithelial lining of the groove that originates from endoderm forms the urethral plate.

Distally, the urethral groove terminates, but the urethral plate continues to grow. At the end of third month, the two urethral folds grow toward one another and close over the urethral plate and fuse in midline. This fusion begins proximally and eventually occurs distally toward the glans. So folding of the urethral folds that close over the urethral plate converts the urethral groove into a tubular penile urethra (**Figure 1-3**). This tubular canal does not extend to the tip of the phallus. The most distal part is formed during the fourth month of embryogenesis.

FIGURE 1-2

Differentiation begins. Early sexual dichotomy under the influence of androgens or estrogens and formation of the urethral plate.





In females, in the absence of dihydrotestostereone, the primitive perineum does not lengthen and fusion of the labioscrotal and urethral folds does not occur. These will respectively form the *labia majora and minora*. Estrogens stimulate the development of the external genitalia of the female. The genital tubercle elongates very slightly, and the phallus bends inferiorly and becomes the clitoris. It should be kept in mind that although the genital tubercle does not elongate extensively in the female, it is generally larger than in the male in the early stages of development, making the use of genital tubercle length very unreliable as a criterion for predicting gender in prenatal ultrasound. The urogenital groove remains open and forms the vestibule of the vagina.

The detailed sexual dichotomy of the external genitalia is summarized in **Figure 1-4**. Analogous embryonic derivatives with male and female counterparts are summarized in **Table 1-1**.



TABLE 1-1 Embryonic structures and their male and female derivatives of the
external genitalia.

Presumptive Structure	Male Structure	Female Structure
Genital tubercle	Glans penis Corvus cavernosa of penis Corpus spongiosum of penis	Glans clitoris Corpus cavernosa of clitoris Bulbospongiosum of vestibule
Urogenital folds and urethral plate	Penile urethra/ventral penis	Labia minora
Labioscrotal folds	Scrotum	Labia majora

The formation of the human urethra at the glans at this stage is unclear. Either the ectodermal cells from the tip of the glans penetrate inward and form a short epithelial cord known as the external urethral meatus, or, as was shown in recent studies, growth of the endodermally derived bladder urothelium toward the skin occurs as a solid urethral plate extending to the very tip of the glans and then canalizing to form the glans urethra and meatus³ (**Figure 1-5**). This means that the classical ectodermal ingrowth theory has recently been challenged by the endodermal differentiation theory. This new theory is based on the results of immunohistochemical staining for cytokeratins. The study concludes that the urethral plate extends to the tip of the phallus and maintains patency and continuity throughout urethral development. This means that the epithelium of the entire urethra originates from the urogenital sinus (endoderm). The cells in the future distal glandular urethra undergo
trans-differentiation into stratified squamous epithelium. Hence, the endodermal theory of urethra formation may explain the embryologic origin of the urethra and the adult histology of the urethra. By 18 to 19 weeks of gestation, formation of the urethra is complete, with subsequent closure of the ventral aspect of the foreskin, thereby completing glans and foreskin formation.





In patients who have failure of fusion of the urethra and/or foreskin, the resulting defect is called hypospadias.⁴ Hypospadias can be described by abnormal ventral placement of the urethra opening anywhere along the glans, the shaft of the penis, the scrotum, or perineal. Hypospadias is also defined by abnormal fusion of the ventral foreskin or abnormalities in the urethral spongiosum. Variations of hypospadias are well documented where the glans and the urethra are normal but the penile shaft urethra is atretic, the so-called "chordee hypospadias" or "hypospadie sans hypospadie."⁵

In male patients who have suboptimal androgen stimulation or lack of functioning androgen receptors, penile development may be inhibited, and the constellation of hypospadias findings may often result (**Figure 1-6**).



In the abnormality of complete androgen insensitivity syndrome, the penis does not develop at all. This is secondary to a defect in the androgen receptor, rendering it non-functional. In fact, on gross appearance, the clitoris in patients with complete androgen insensitivity syndrome appears normal, although subtle differences exist. These observations have been made in both humans as well as animal models, consistent with the theory that female development is not a default pathway but an active process.^{7, 8} Interestingly, females without the normal stimulation from the *SRY* gene on the Y chromosome can also develop into a male pattern under the influence of either endogenous and/or exogenous androgens. For example, it is well known clinically that patients with congenital adrenal hyperplasia such as enzymatic defects in 21-alpha-hydroxylase and 11-beta-hydroxylase can have varying degrees of virilization or even normal-appearing male phallic structures.²

In females, although both 5-alpha-reductase and androgen receptors are expressed, they do not develop male external genitalia due to their low levels of androgens. Even though the early steps of genital tubercle and urethral plate formation occur in females, the lack of dihydrotestosterone means that the genital tubercle and urethral plate do not lenghten and the urethral folds do not fuse. Although it is well known that disruption of androgen signaling can result in feminization of male genitalia and excess androgen can cause virilization of the female genitalia, little is known regarding molecular embryology. Clinically, the former often results in hypospadias or micropenis, whereas the latter can present as cliteromegaly.

Androgens (testosterone and dihydrotestosterone) and estradiol signal by means of androgen receptor (AR) and estrogen receptors (ER α and ER β), respectively. When activated by ligand binding, ER and AR translocate from the cytoplasm to the nucleus, where they can bind DNA directly to affect transcription of target genes. Although the long-standing dogma is that the sexually indifferent genital tubercle is masculinized by androgens and that feminization is a default state that occurs in the absence of androgen activity, recent studies of ER mutants have falsified this hypothesis (**Figure 1-6**). Homozygous null mutant mice for ER α have an elongated clitoris that contains a bone (os clitoris) several times longer than that of wild-type females.⁷ Thus, in the absence of ER α activity, female external genitalia are partially masculinized, suggesting that estrogen is required for inhibition of clitoral growth in females. This raises the intriguing possibility that basal levels of androgen in females can lead to masculinization of the genital tubercle, and estrogen is required to counter the influence of androgen.

Mutations in the androgen receptor cause feminization of the external genitalia. Mutations in the gene that encodes 5α -reductase 2, which converts testosterone into dihydrotestosterone, also disrupts masculinization of the genital tubercle and causes defects ranging from hypospadias and micropenis to complete feminization of the external genitalia.⁹ Taken together, these results suggest that the balance of androgens to estrogen is a critical factor in determining sexual differentiation of the genitalia. Little is known about the interactions between these systemically circulating hormones and the locally expressed genes involved in patterning of the genital tubercle. There are many examples highlighting the potential strong genetic pathways to be influenced by sex steroids. It seems likely that the same phenotypes (e.g. hypospadias) can be induced either by exposure to endocrine disrupting chemicals or by mutations, but the former may leave no genetic signature.

Not surprisingly, penile curvature—or so-called "chordee"—which is a normal part of development with the penile straightening typically occurring by 20 weeks of gestation, is also known to be a common congenital anomaly⁶ (**Figure 1-7**). Congenital penile curvature can be explained as an arrest in normal development and is often associated with hypospadias. The most common etiology is an abnormality in the growth of the ventral skin of the penis, with resulting ventral penile curvature. Less common is actual corporal disproportion where the dorsal aspect of the corporal bodies grows normally while the ventral aspect is tethered. Finally, the most rare form of congenital curvature is an abnormality of the urethral and surrounding spongiosum. This can result in a paper-thin urethra with ventral tethering that will require replacement and augmentation during reconstruction.

FIGURE 1-7

Ventral curvature of normal penile development.



courtesy L. Baskin

1.2 Cellular and Molecular Mechanisms

Over the past decade, the genetics of external genital development have begun to be understood. The early tubercle has a superficial resemblance to the limb bud, but an important distinction is that the limb consists of only mesoderm and ectoderm, whereas the genital tubercle also has an endodermal component, the urethral epithelium.¹⁰ The role of the distal end of the urethral plate epithelium in promoting the outgrowth of the genital tubercle is in some ways similar to that of the apical epidermal ridge of the limb bud. In mice, if the ventral urethral plate is removed, the genital tubercle becomes hypoplastic. Urethral epithelium, which expresses Sonic hedgehog (shh), acts as a signaling region that controls outgrowth and pattern formation, and ultimately differentiates into the urethral tube.

Sonic hedgehog is released by the entire urethral plate. It is the best-studied ligand of the hedgehog signaling pathway and plays a key role in regulating vertebrate organogenesis, such as in the growth of digits on limbs and in early genital and urethral development. In shh-null mice, genital tubercle development is arrested at the initial outgrowth stage (**Figure 1-8**).

FIGURE 1-8

Summary of key epithelial and mesenchymal genes involved in early genital tubercle development. Underexpression or deletion of key genes results in abnormal genital development.



Sonic hedgehog from the urethral plate also upregulates *Hoxa13* and *Hoxd13* expression within the genital tubercle mesenchyme.¹¹ The expression of these two hox genes is required for the development of the early cloaca and genital tubercle. Differentiation of the erectile and connective tissues of the tubercle is organized around the urethral plate, which suggests that the urethral plate could be a signaling region that confers polarity to the adjacent mesenchyme.¹²

Initially, shh-dependent expression of fibroblast growth factor (*Fgf8*) was thought to be essential for genital tubercle growth.¹³ However, later it was shown that genetic deletion of Fgf8 in the genital tubercle has no effect on external genital development.¹⁴ Indeed, analysis of Fgf8 target genes and the distribution of Fgf8 protein showed that Fgf8 is not even translated in the urethral epithelium.¹⁴ Although previous *in vitro* experiments suggested a role for Fgf8 in the genital tubercle,¹³ genetic studies *in vivo* showed that Fgf8 is not involved in genital development.¹⁴ These findings highlight a key difference in the role of Fgf signaling between limbs and genitalia.

Two critical morphogenetic processes are involved in urethral tube closure: ventrolateral growth of the preputial swellings to form the foreskin and remodeling of the bilaminar urethral plate into an epithelial tube. Hypospadias can theoretically occur when either of these processes is disrupted.

Shh not only has an important role in the early genital tubercle, but also has a role in regulating Fibroblast growth factor 10 (Fgf10) expression, which is important in closure of urethra later.¹⁵ Hoxa13 is also expressed in the urethral plate, and deletion of Hoxa13 also results in hypospadias.¹⁶ Bone morphogenic protein7 (bmp7), which is a member of the transforming growth factor beta superfamily, and fibroblast growth factor 8 (Fgf8) are released by the distal urethral plate adjacent to the site of the forming genital tubercle. Functional studies have implicated bmp7 in the development of a closed urethral tube and elongation of the urethral plate, as well as in the septation of the cloaca.¹⁷ Ephrins and their receptors have also been implicated as playing a role in this closure process. Loss of either ephrinB2 or the receptors EphB2 and EphB3 leads to severe hypospadias and persistence of the cloaca.¹⁸

In addition, genital development may be under partial control of epigenetic mechanisms. Recent *in vitro* studies suggest that expression of several genes involved in genital tubercle differentiation and development when suppressed by estrogen can have their expression rescued by inhibiting DNA methylation (**Figure 1-9**). DNA methylation is a principal epigenetic mechanism regulating many diverse cell processes. This kind of observation may provide a mechanistic basis for environmental hormonal effects on external genital maldevelopment, even in the absence of overt gene mutations.¹⁹



In conclusion, our understanding of the mechanisms of genital development still lags far behind the limb, and major questions remain to be answered, including the molecular nature of the signals that initiate genital budding, outgrowth, tissue polarity, and tubulogenesis of the urethra.

1.3 Anatomy of the Penis

After development has been completed, the penis is in an uncircumcised state and consists of the penile shaft, the glans penis, along with the coronal sulcus and the completed foreskin (**Figure 1-10**). It is normal in the newborn period for the foreskin to remain adhesed to the glans, with the urethral meatus often being difficult to visualize. Postnatal elevation of testosterone, peaking approximately at age 3 months and normal physiologic erections, which occur during gestation and postnatally, will ultimately facilitate natural breakdown of the adhesions.



The penile body is composed of the corpus spongiosum, a well-developed erectile structure that surrounds the urethra. The corpus spongiosum lies central and inferior to the two corporal cavernosa bodies. A thick connective tissue layer, the tunica albuginea, is composed of elastin and collagen and covers the paired corpora cavernosa bodies. The neuroanatomy of the penis has been well described with the dorsal nerve fanning out from the penile hilum along the corpora cavernosa bodies, to the junctions of the corpus spongiosum (**Figure 1-11**).²⁰ The dorsal penile nerves provide primary sensation for the penile shaft and glans. There is a paucity of nerves at the 12 o'clock position, with the penile neurovascular bundle lying at the 11 and 1 o'clock positions and extending circumventrally to the 5 and 7 o'clock positions where the corpora cavernosa meets the corpus spongiosum.²¹ The nerves terminate within the glans penis, and the distribution remains consistent in both the normal penis and patients with hypospadias. Their positioning has implications for penile straightening, where the 12 o'clock position, which is void of nerves, is an ideal area for dorsal plication for the correction in most patients with mild and moderate penile curvature both with and without hypospadias (**Figure 1-12**).

FIGURE 1-11

Ventral-lateral view (top) and Dorsal-lateral (bottom) views showing 3-dimensional (3D) reconstruction of penile neuroanatomy.





FIGURE 1-12

Schematic representation for dorsal plication for correction of penile curvature.



In humans, the growth of the penis occurs in four stages:

- 1. During pregnancy, when the penis reaches an average length of 3.5 cm in the newborn.
- From birth to age 2 years when the penis grows an additional ~1.5 cm, under the influence of the so-called "mini puberty" with maximum levels of androgens occurring at 3 months postnatally.
- **3.** From age 2 to 11 years, the so-called "postnatal non-androgen growth stage," when the penis reaches an average length of 6.5 cm, adding an additional 1.5 cm.
- Post-pubertal when under the influence of pubertal androgen, the penis reaches its final adult length.²²

1.4 Anatomy of the Clitoris

As the clitoris arises from the same embryologic structure, it is not surprising that the clitoris has many similar anatomical features to the penis.² *Knowledge of clitoral innervation is an absolutely critical underpinning of any modern reconstructive surgery of this organ.* The neuronal innervation of the clitoris is analogous to the penis, with an extensive distribution of nerves surrounding the clitoral bodies that innervate the glans clitoris (**Figure 13**). The dorsal nerve, also like the penis, fans out to cover the lateral surfaces of the clitoral body. As in the penis, there is a lack of nerves at the 12 o'clock position. In addition, the ultrastructure of the erectile tissue within the clitoral body is similar to that of the penis.²

FIGURE 1-13

3D reconstruction of clitoral anatomy showing extensive neuroanatomic innervation (red) of the glans clitoris (green).



1.5 **Development of the Testes**

Sexual developmental dimorphism in humans starts between the 6th and 7th week of gestation and ends approximately in the 20th week when a male or female phenotype is recognized. As a result of complex interactions between endocrine, paracrine, genetic, and mechanical processes, gonads differentiate into testes or ovaries and descend to their physiological position. Testicular descent is essential, as it assures that the temperature is kept lower than the regular body level of 37°C, which is vital for regular sperm production. Cryptorchidism, the absence of one or both testes from the scrotum, affects about 3.5% of full-term male newborns, the incidence of which decreases to 1% postnatally during the first few months.

Determination of genetic sex is caused by inheritance of either a Y or X chromosome from the male gamete. Primary germ cells appear in the extra-embryonic tissues encircling the yolk sac. From the 3rd week of gestation, they migrate through the caudal umbilical stalk into the urogenital ridge. Roughly in week 5 of gestation, the genital (or gonadal) ridge appears after condensation of meso-dermal cells and overlying epithelium. After migration into the mesenchyme, these epithelial cells develop into the seminiferous tubules. A large number of genes are associated with the differentiation of the genital ridge; they are responsible for the distinction and promotion of gender-specific sexual development including WT1, SOX9, FGF9, and SRY (**Table 1**-2). Primordial gonadal tissue develops from this intermediate mesoderm located along the gonadal ridge on either side. Controlled by the testis-determining SRY gene—the sex-determining gene on the Y chromosome—primary bipotential gonadal tissue differentiates into a testis from the 6th week of gestation onward. This *SRY* gene encodes a transcription factor, which is a member of the SOX gene family. This transcription factor is assigned to the sex-determining region Y protein, initiating male sex determination.

Genes	Name, function	Mutations
SRY	Sex-determining gene (region Y) initiates male sex determination, differentiation of Sertoli cells	Gonadal dysgenesis, XX male syndrome, etc.
WT1	Wilms' tumor protein, urogenital development	Testicular cord disruption
FGF9	Glia-activating factor, Sertoli cell differentiation	Reversal of gender
PGD2	Prostaglandin D2, feedforward loop with Sox9	Predomination of the female pathway
SOX9	SRY (sex-determining region Y)-box 9, regulates transcription of the anti-Müllerian hormone gene	Reversal of gender
AMH	Anti-Müllerian hormone	Persistent Müllerian duct syndrome

TABLE 1-2 Genes involved in testes development.

Regression of the Müllerian ducts starts off from the 8th week of gestation after Sertoli cells begin to produce Müllerian inhibitory hormone. In the absence of Sertoli cells, Wolffian ducts undergo apoptosis while Müllerian ducts develop and differentiate into the female reproductive system. Anti-Müllerian hormone interacts with specific receptors (e.g. the AMH type II receptor of the fetal Müllerian ducts) to induce programmed cell death. From week 10 onward, Leydig cells produce insulin-like protein 3 (INSL3) and androgens, which are essential for the differentiation of the Wolffian duct and in particular for testicular descent. Secretion of testosterone by Leydig cells is necessary to promote masculinization of the embryo, especially for the differentiation of the Wolffian duct into the epididymis, ductus deferens, and seminal vesicle. The Wolffian or mesonephric duct derives from the pronephros connecting the primitive kidney or mesonephros with the cloaca.

1.5.1 **Transabdominal descent of the testes**

Testicular descent can be divided into a first and second stage: the transabdominal and the inguinoscrotal, both characterized by two morphologically as well as hormonally distinct steps. The intra-abdominal migration of the testes between the lumbar area and the inner inguinal ring occurs during the first trimester after conception. It is directed by a non-androgenic hormone factor, ISNL3. Insulin-like protein 3 is produced by the Leydig cells and is essential for the transabdominal testicular descent into the scrotum. It stimulates growth of the genito-inguinal ligament, a fold of the mesorchium containing the gubernaculum testis (**Figure 1-14**).

The enlargement of the gubernaculum between the 8th and the 15th week of gestation anchors the testes passively near the groin while the abdomen enlarges (**Figure 1-15A**). However, the cranial suspensory ligament, a residual of the cranial mesentery of the urogenital ridge, eventually regresses due to the influence of testosterone. In fact, this would mean that the transabdominal descent of the testes equals a tethering of the gonads to the groin as the abdominal cavity enlarges and kidneys migrate cranially (**Figures 1-14B** and **1-15B**).

The swelling of the gubernaculum is caused by cell proliferation and accumulation of glycosaminoglycans and hyaluronic acid regulated by ISNL3. Disruption of the ISNL3 genes results in intraabdominal testes and malformation of the gubernaculums, whereas overexpression of ISNL3 in female mice causes descent of the ovaries.



FIGURE 1-15

Human embryonic sections showing the change in position of the testes and relative relationships of the gubernaculum and epididymis during testicular descent: 12 weeks' gestational age (A); 15 weeks' gestational age (B).



12th week gestation

15th week gestation

1.5.2 **Inguinoscrotal descent of the testes**

The second stage of testicular descensus takes place during the third trimester of gestation. Under the guidance of the gubernaculum, the testes descend through the inguinal canal into the scrotum. Conditions for this second descensus between the 26th and 28th week of gestation is a dilatation of the canal by the swollen gubernaculum (bulb), a developed processus vaginalis, and some abdominal pressure. Already from the 8th week of gestation, the inguinal canal develops as caudal evagination of the abdominal wall, representing the processus vaginalis. This inguinoscrotal hernia incorporates the gubernaculum, which occurs as a central mesenchymal column and an outer parietal layer. After completed descensus, the gubernaculum involutes and remains as a fibrous connective tissue attaching the testis to the lowest point of the scrotum. This process is androgen dependent, although the exact mechanism remains unknown. Testosterone seems to affect the genitofemoral nerve. In return, this nerve secretes calcitonin gene-related peptide, a neurotransmitter that may provide chemotactic signals to control inguinoscrotal gubernacular migration via rhythmic contractions of the gubernaculum.⁶



1.6 **References**

- 1. Blaschko SD, Cunha GR, Baskin LS. Molecular mechanisms of external genitalia development. Differentiation; research in biological diversity. Differentiation. 2012;84(3):261–268.
- 2. Baskin LS, Erol A, Li YW, et al. Anatomical studies of the human clitoris. J Urol. 1999;162(3 pt 2):1015–1020.
- 3. Kurzrock E, Baskin L, Cunha G. Ontogeny of the male urethra: theory of endodermal differentiation. 1999;64(2):115–122.
- 4. Baskin LS, Erol A, Li Y, et al. Urethral seam formation and hypospadias. Cell Tissue Res. 2001;305(3):379-387.
- 5. Baskin LS, Ebbers MB. Hypospadias: anatomy, etiology, and technique. J Pediatr Surg. 2006;41(3):463–472.
- 6. Baskin L, Duckett J, Lue T. Penile curvature. Urology. 1996;48(3):347-356.
- 7. Yang JH, Menshenina J, Cunha GR, *et al.* Morphology of mouse external genitalia: implications for a role of estrogen in sexual dimorphism of the mouse genital tubercle. J Urol. 2010;184(4 suppl):1604–1609.
- 8. Wilson JM, Arnhym A, Champeau A, et al. Complete androgen insensitivity syndrome: an anatomic evaluation and sexual function questionnaire pilot study. J Pediatric Urol. 2011;7(4):416–421.
- Sinnecker GH, Hiort O, Dibbelt L, et al. Phenotypic classification of male pseudohermaphroditism due to steroid 5 alpha-reductase 2 deficiency. Am J Med Genet. 1996;63(1):223–230.
- 10. Cohn MJ. Development of the external genitalia: conserved and divergent mechanisms of appendage patterning. Dev Dyn. 2011;240(5):1108–1115.
- Lin C, Yin Y, Veith GM, et al. Temporal and spatial dissection of Shh signaling in genital tubercle development. Development. 2009;136(23):3959–3967.
- 12. Perriton CL, Powles N, Chiang C, *et al* Sonic hedgehog signaling from the urethral epithelium controls external genital development. Dev Biol. 2002;247(1):26–46.
- 13. Haraguchi R, Mo R, Hui C, *et al.* Unique functions of Sonic hedgehog signaling during external genitalia development. Development. 2001;128(21):4241–4250.
- 14. Seifert AW, Yamaguchi T, Cohn MJ. Functional and phylogenetic analysis shows that Fgf8 is a marker of genital induction in mammals but is not required for external genital development. Development. 2009;136(15):2643–2651.
- Petiot A, Perriton CL, Dickson C, et al. Development of the mammalian urethra is controlled by Fgfr2-IIIb. Development. 2005;132(10):2441–2450.
- Morgan EA, Nguyen SB, Scott V, et al. Loss of Bmp7 and Fgf8 signaling in Hoxa13-mutant mice causes hypospadia. Development. 2003;130(14):3095–3109.
- 17. Wu X, Ferrara C, Shapiro E, *et al.* Bmp7 expression and null phenotype in the urogenital system suggest a role in re-organization of the urethral epithelium. Gene Expr Patterns. 2009;9(4):224–230.
- Yucel S, Dravis C, Garcia N, et al. Hypospadias and anorectal malformations mediated by Eph/ephrin signaling. J Pediatr Urol. 2007;3(5):354–363.
- Aitken KJ, Jiang J, Bechbache M, et al. Epigenetic mechanisms direct estrogen-induced downregulation of gene expression and cell biological processes critical for genital tubercle formation. Presented at the 2012 annual conference and exhibition of the American Academy of Pediatrics; October 20–23, 2012; New Orleans, LA.
- 20. Baskin LS, Lee YT, Cunha GR. Neuroanatomical ontogeny of the human fetal penis. Br J Urol. 1997;79(4):628-640.
- 21. Baskin LS, Erol A, Li YW, et al. Anatomical studies of hypospadias. J Urol. 1998;160(3 Pt 2):1108–1115.
- 22. Gallo CB, Costa WS, Furriel A, et al. Development of the penis during the human fetal period (13-36 weeks post-conception). J Urol. 2013;190(5):1876–1883.





Cryptorchidism, Hernia, and Hydrocele

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2.1 Cryptorchidism—An Overview

Cryptorchidism, also commonly referred to as undescended testicle, is one of the most common congenital anomalies diagnosed in males. Although the diagnosis is seemingly straightforward (i.e., gonad is not palpable at the normal anatomical position, the most dependent portion of its respective hemi-scrotum), it is important to establish some definitions in order to understand classification nomenclature frequently employed in the literature:

Congenital versus acquired cryptorchidism. The distinction is solely based on findings documented during the neonatal exam. In congenital cases, the gonad is not in the scrotum at birth, while an acquired testicle is in a normal location at birth but not later on in life. Acquired cryptorchidism may refer to both iatrogenic causes, such as with entrapment after herniorraphy, or spontaneous causes. When the cause is spontaneous, the testis is referred to as an ascended testis.

Retractile testis. A retractile testis refers to a gonad that intermittently migrates to a higher location along the path of normal descent, believed to be due to an active or brisk cremasteric reflex. By definition, the testicle can be manipulated down to its normal location during exam, and remains there for some time after releasing it.

"Truly" undescended versus ectopic testis. A testis is considered ectopic if its location (as determined during physical exam and/or surgery) is outside of the scrotum and not within the normal path of descent between the abdomen and scrotum. An ectopic position is most commonly documented in the superficial inguinal pouch (anterior to the external oblique fascia and adjacent to the external inguinal ring) or, more rarely, in a pre-pubic, femoral, perineal, or contralateral scrotal position. Although sometimes a difficult distinction, an ectopic testicle is unlikely to spontaneously descend to a normal location or respond to hormonal stimulation.

Palpable versus non-palpable testicle. The inability of the examiner to feel the gonad during physical exam (including exam under anesthesia) indicates a non-palpable testis. If non-palpable, considerations expand to the inability to palpate due to an intra-abdominal location, inaccurate exam, and absence or atrophy due to a prenatal insult or lack of development. The diagnosis is confirmed during exam under anesthesia, the first step of any surgical procedure for cryptorchidism.

2.2 Epidemiology

When assessed in the newborn period, the incidence is somewhat variable yet clearly dependent on gestational age, being diagnosed in 1.0% to 4.6% of full-term and 1.1% to 45.3% of preterm male neonates.¹ In up to one-third of cases, the condition may affect both gonads.² Following spontaneous decent, often seen in the first 3 to 6 months of life, prevalence stabilizes at 0.7% to 1.0% of 1-year-old boys. Similarly, an ascended testis is found in approximately 1.5% of pre-pubertal boys, with up to 77% showing spontaneous descent at puberty.³ However, these numbers can show wide variation between studies and time periods, which highlights potential differences between populations and

disease severity along with inclusion of different proportions of patients within the above-mentioned categories (particularly children with retractile testicles, mislabeled as undescended or ascended gonads).

Cryptorchidism is a component of almost 400 syndromes, many with important comorbidities that often raise concerns for surgical correction when anesthetic risks are considered. Nevertheless, the condition is most commonly seen in otherwise healthy children. Currently, the thought is that testicular maldescent is polygenic and multifactorial, with evidence of a familial predisposition in boys with affected twins, brothers, and fathers.^{4,5} Environmental exposures are also potential etiological factors, including environmental chemicals—such as phthalates, polychlorinated pesticides, and polybrominated flame-retardants—as well as maternal alcohol consumption and tobacco use during pregnancy. On a greater scale, cryptorchidism has been included in the so-called "testicular dysgenesis syndrome," which includes other male genitourinary disorders, such as hypospadias, testicular cancer, semen production abnormalities, and infertility,⁶ linked together by potential common pathogenic mechanisms that interfere with normal fetal testis development.

2.2.1 **Diagnosis/evaluation**

There are three factors on clinical history and physical examination that raise the diagnosis of cryptorchidism: birth exam findings, scrotal asymmetry, and prematurity.⁷ Primary care health care providers can use these variables to heighten their level of suspicion; nevertheless, a child with suspected cryptorchidism should be referred for evaluation by a surgical specialist in a timely fashion, irrespective of other historical confounders. When patients with a normal exam or retractile testicles are excluded, approximately 75% of undescended testes are palpable and unilateral.⁸ One large series provides guidance as to the expected location of gonads: Docimo *et al.* reported testes inside the abdominal cavity in 33.8%, near the internal ring (so-called "peeping") in 11.8%, canalicular in 27.3%, and the remaining beyond the external ring, most commonly in an ectopic location (the superficial inguinal pouch).⁹

The main method and standard for diagnosis is careful physical exam, done in the clinic with the child in supine, upright cross-legged, and—if developmentally possible—standing positions, followed by confirmation of incomplete descent to a dependent scrotal location after induction of general anesthesia. Careful examination of the groin, femoral region, perineum, contralateral scrotum (to detect the rare cases of transverse testicular ectopia), and pubic areas are needed in order to correctly classify a testis as palpable or non-palpable, a critical step that influences further diagnosis and treatment. Gentle downward pressure along the ipsilateral inguinal canal from the anterior iliac spine to the scrotum and palpation with the opposite hand helps to identify the lowest position of a palpable testis (Figure 2-1). Repeated examinations, patient distraction techniques, a warm environment, and use of hand lotion or liquid soap as a lubricant for the examiner's hands help determine testicular position. Examination should include documentation of testicular palpability, position, mobility, size, and possible associated findings such as hernia, hydrocele, penile size, and urethral position. In addition, the size and location of the normally located contralateral gonad (in unilateral cases) can have important prognostic implications, as the presence of compensatory hypertrophy (length greater than 2 cm in pre-pubertal young boys) is highly associated with monorchia.¹⁰ Size may be measured by calipers, orchidometer, or ultrasound.

Associated genital exam findings may warrant specific diagnostic tests. Particularly, if both testes are non-palpable and/or if associated penile abnormalities are detected, karyotype and a hormonal profile (including 17-hydroxyprogesterone levels) should be performed.

A newborn with male external genitalia but bilateral non-palpable gonads is potentially a genetic female (46,XX), with a disorder of sex development (DSD; congenital adrenal hyperplasia), until proven otherwise. The implications of a delayed or missed diagnosis in this circumstance can be tragic, as a high proportion of patients with this condition are unable to regulate their electrolyte levels and may present later in shock, hyponatremia, and hyperkalemia.¹¹ Also, proximal hypospadias and cryptorchidism have been found to be associated with an important frequency of chromosomal abnormalities.¹² If penile size is particularly small (less than 2 standard deviations), measurement of testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels in the first few months of life is warranted, in order to detect problems in the hormone production axis or raise the suspicion of anorchia (a diagnosis that should always be confirmed by surgical exploration with documentation of blind-ending spermatic vessels in the abdomen, inguinal canal, or scrotum).

Except for very select and specific clinical scenarios, there is no need for imaging studies to further evaluate cryptorchidism. Commonly, an ultrasound examination is contemplated, as the study is considered to be innocuous and thought to help localize a non-palpable gonad while reassuring parents of the diagnosis. Nevertheless, the practice of imaging for undescended testis is time consuming, resource draining, and ultimately may be clinically misleading. If the testicle is palpable, the information obtained adds little to the physical exam. In cases of retractile gonads, an ultrasound is notorious for being unable to differentiate it from an inguinal testicle. Lastly, in cases of non-palpable cryptorchidism, the study lacks the diagnostic performance to confidently locate the testicle or confidently establish the absence of an intra-abdominal testicle.¹³ The main exception is for evaluating children with suspected diagnosis of DSD, as an ultrasound can help determine the presence of Müllerian structures.¹⁴ In some circumstances, such as previous inguinal surgery and/or obesity, evaluation with magnetic resonance imaging or ultrasound may help guide the best initial surgical strategy. This, however, has to be taken in the context of added cost and modest value, considering that surgical exploration is likely warranted despite radiological findings.

FIGURE 2-1

Physical exam for a child with cryptorchidism. Note the use of lubrication and gentle pressure following the inguinal path of expected descent while the contralateral hand feels the scrotum and low inguinal region.

(Photo courtesy of Armando Lorenzo, MD)



2.2.2 **Recommendations, diagnosis, and evaluation** of cryptorchidism

- A well-documented neonatal physical exam is important to diagnose and plan for management of cryptorchidism (standard of care)
- The prevalence of cryptorchidism decreases during the first year of life, and is more pronounced in premature infants (level of evicence [LOE] 2)
- Bilateral non-palpable testicles in a newborn should be considered to represent a diagnosis of DSD and prompt evaluation for congenital adrenal hyperplasia is recommended (LOE 3)
- Testicular ascent is a true pathological entity and does not necessarily represent a missed diagnosis early in life. These children should be candidates for timely surgical correction, similar to patients diagnosed early in life (LOE 3)
- Ultrasound assessment plays little role and has a modest to poor diagnostic performance in the routine assessment of children with cryptorchidism (LOE 1)

2.3 Roles of Hormones in Cryptorchidism

Cryptorchidism accompanies defects in the hypothalamic-pituitary-testicular axis and is associated with environmental endocrine disruptors. Thus, cryptorchidism can be viewed as an endocrinopathy that might be responsive to hormonal manipulation. The potential role for hormonal therapy in the treatment of cryptorchidism arises from the dependency of testicular descent on androgens. Transabdominal descent may be controlled by Müllerian inhibiting substance,¹⁵ whereas inguinoscrotal descent appears to be androgen-dependent,^{15,16} and is mediated by calcitonin gene–related peptide (CGRP). Androgens act on the genitofemoral nerve, which releases CGRP, causing rhythmic contractions of the gubernaculum.

2.3.1 **Diagnosis**

In boys with unilateral or bilateral cryptorchidism where one testis is palpable, no further laboratory evaluation is necessary.¹⁷ In patients 3 months or younger with bilateral non-palpable cryptorchidism, LH, FSH, and testosterone levels can help determine if testes are present. After 3 months of age, human chorionic gonadotropin (hCG) stimulation (100 IU/kg) is usually sufficient to detect a rise in serum testosterone 4 to 5 days later.¹⁸ A failure to see a measurable increase in testosterone in combination with elevated LH and FSH is consistent with the diagnosis of anorchia.^{19,20} Thorup and colleagues further refined the serologic evaluation of bilateral non-palpable testes.²¹ There are preliminary data that a single serum sample, without hCG stimulation, demonstrating low inhibin-B and elevated gonadotropins is indicative of bilaterally absent testes or non-functional nubbins.

2.3.2 **Treatment**

Most studies on the effectiveness of hormonal therapy have assessed the effectiveness of hCG²²⁻²⁸ or luteinizing hormone releasing hormone (LHRH)^{24,25,28-34} in inducing testicular descent. Only one study has examined long-term fertility outcomes and found that adjuvant buserelin administration after orchidopexy improved semen analyses compared with controls.³⁵ Overall, most studies were of fair to poor quality, and were heterogeneous with respect to patient populations, testis location, and dosage and schedules of hormone administration. Studies of the comparative effectiveness of hCG and LHRH have demonstrated inconsistent results, but generally indicate that 2% to 14% of true undescended testes descend with hormonal stimulation and remain descended 3 to 6 months after cessation of treatment.^{24,25,28,36}

2.3.3 **hCG**

The action of hCG is virtually identical to that of LH and also has mild FSH activity. Human chorionic gonadotropin induces production of steroid hormones by stimulating Leydig cells to produce androgens. Pharmacologically, hCG is administered by intramuscular injection. Multiple series have been published, but divergent results have been observed, likely due to differences in patient age, treatment schedules, and possible inclusion of retractile testes. Success rates of 25% to 67% for descent of undescended testes into the scrotum after hCG administration have been reported.^{22,24,27,37} Testis location is an important determinant of success. with testes located closer to the scrotum more likely to respond to treatment.

Different schedules, ranging from 3 to 15 doses of various doses, have been reported.^{28,38-40} No differences in testicular descent were observed between 1500 IU versus weight-based dosing up to 3000 IU every other day for 14 days.²⁶ Similar response rates were observed with doses of 500 IU once a week and 1500 IU three times a week.²² However, dosing frequency may affect testicular descent rates. Hesse *et al.*²⁷ reported a greater proportion of testes descended following administration of two lower-dose hCG injections per week for 5 weeks compared with one higher dose injection every 7 to 10 days for 3 weeks. Repeated courses following an unsuccessful first trial of hCG have offered little advantage.

Short-term side effects of hormone treatment, including hCG, include increased scrotal rugae, pigmentation, pubic hair, and penile growth, which regress after treatment cessation.²⁸

2.3.4 LHRH analogs

Luteinizing hormone releasing hormone or gonadotropin releasing hormone (GnRH) analogs stimulate the release of the pituitary gonadotropin LH, resulting in a temporary increase of gonadal steroidogenesis. These hormones are available as a nasal spray, but they are only approved for the treatment of cryptorchidism in Europe. Success rates range from 9% to 62%; however, similar to the studies on hCG, interpretation of results is limited by multiple treatment strategies and heterogenous patient populations.^{30,32–34,40–42} In the one good quality randomized controlled trial comparing hCG 3300 IU per week for 4 weeks with GnRH spray 200 mcg 6 times a day for 4 weeks, Rajfer *et al.*²⁸ reported testicular descent into the scrotum in 6% of the hCG group and 19% of the GnRH group. This was not statistically significant. In another fair quality randomized trial comparing LHRH to placebo, 141 boys aged 2 to 12 years were randomized to LHRH 0.4 mg or placebo intranasal 3 times a day for 4 weeks. In the LHRH arm, 9.7% of participants were observed to have testicular descent compared with 1.6% in the placebo arm, but the difference was not statistically significant.³³ In poorer quality studies, a slightly higher proportion of testicular descent was noted with LHRH than with placebo; however, different doses and outcome definitions of testicular descent were used.^{29–32,34,42} Overall, the proportion of testes that remained completely descended following LHRH was low. Proponents of hormone therapy have suggested that initial treatment with GnRH/LHRH may deserve some consideration since it is administered as a spray rather than an injection and may induce descent in more distal testes, make intra-abdominal testes palpable, or help differentiate retractile from true undescended testes. However, the utility of these endpoints can be debated. Additionally, testicular re-ascent has been observed 6 months after completion of treatment.^{30,32} The recognized side effects of increased androgens, including increased penile or testicular size, scrotal erythema, or erections, seem to be less with LHRH than hCG.

2.3.5 **Combined treatment**

Several authors have recommended combined GnRH-hCG hormonal treatment. Lala *et al.* administered LHRH 1.2 mg/day for 4 weeks with hCG 500 IU 3 times a week for 3 weeks to non-responders.⁴¹ After combined treatment, 38% of testes descended. Bica and Hadziselimovic treated patients with a low dose of buserelin 20 mcg daily for 28 days followed by hCG for failures and found that 26% of the testes descended with the spray alone, while hCG increased the descent to 37%.²³ Consequently, Hadziselimovic *et al.* proposed initial treatment with GnRH spray 400 mcg 3 times a week for 4 weeks followed by hCG 1500 IU weekly for 3 weeks for those who did not respond.⁴³ A success rate of 56% with GnRH was increased to 65% with the addition of hCG.

2.3.6 **Adjuvant therapy**

Administration of LHRH in boys who had no germ cells on testicular biopsy at the time of orchidopexy did not show improvement on repeat biopsy after LHRH, but those who had some germ cells demonstrated improvement.⁴⁴ Similarly, GnRH/LHRH combined with hCG administration prior to orchidopexy has been shown to improve the fertility index on histopathologic analysis of biopsies obtained at the time of orchidopexy.^{45,46} Adjuvant hCG treatment alone has not been shown to improve fertility indices and has been associated with increased germ cell apoptosis.⁴⁷ Although it is unknown if this effect on testis histology persists into adulthood or disappears once the hormonal stimulus is removed, Hadziselimovic and Herzog showed that men who were treated in childhood with LHRH had better semen analyses compared with men who had childhood orchidopexy alone or placebo treatment.³⁵ Hormone therapy may improve fertility indices⁴⁸ and could theoretically have a role as neoadjuvant or adjuvant therapy when combined with orchidopexy, but identification of the cohort of patients who would most likely benefit would be difficult and the cost-effectiveness of this approach has not been studied.

2.3.7 **Recommendations: hormonal therapy**

- The effect of hCG or LHRH on testicular descent in undescended testis is mild (<20%), with no observable difference between the two therapies (LOE 1)
- Based on poor quality randomized controlled trials and poor to good quality cohort studies, there is low to moderate strength of evidence for increased testicular descent with LHRH or hCG compared with placebo (LOE 2 and 3)
- Side effects include increased penile or testicular size, scrotal erythema, and erections, which are transient (LOE 2 and 3)
- Studies that compared doses and dosing schedules within hormone type were of poor quality and too heterogeneous to permit drawing any useful conclusions

2.4 Surgical Management of Cryptorchidism

Surgical treatment differs according to the location of the testis, and different orchidopexy techniques have been described. For the purpose of this review, the most common approaches, their indications, success rates, and complications will be discussed.

2.4.1 **Timing for orchidopexy**

There seems to be a general consensus regarding the ideal age for orchidopexy, although an evidencebased guideline is still lacking. According to the 1996 American Academy of Pediatrics recommendation,⁴⁹ orchidopexy should be performed before age 1 year based on changes in the number of germ cells in the undescended testis (UDT) that start to occur beyond that age.⁵⁰

Results from a randomized controlled trial comparing testicular growth after surgery performed at 9 months versus at age 3 years indicated that early orchidopexy was followed by a partial catch-up testicular growth, which was not seen after late operation.⁵¹ These findings, as well as the fact that testicular descent is unlikely to occur in full-term babies after age 6 months,⁵² support the current recommendation of performing orchidopexy between the ages of 6 and 12 months.⁵³

2.4.2 Orchidopexy techniques

2.4.2.1 **Surgical approach to the palpable testis**

2.4.2.1.1 Inguinal orchidopexy

Palpable testes can be approached most commonly through an inguinal incision. The key technical steps of this operation can be described as follows:

- Mobilization of the testis and the spermatic cord to the level of the internal inguinal ring after division of the gubernaculum testis (Figure 2-2).
- 2. Dissection of the spermatic cord by division of the cremasteric muscle and internal spermatic fascia.
- 4. High (proximal) ligation of the processus vaginalis (**Figures 2-3A** and **2-3B**).
- **5.** Further mobilization of the cord allowing placement of the testis in a sub-dartos pouch within the hemi-scrotum, without tension.

FIGURE 2-2

Transverse inguinal incision for management of UDT.



FIGURE 2-3

Mobilization of the spermatic cord after dissection of the processus vaginalis.



2.4.2.1.2 Scrotal orchidopexy

The scrotal approach for management of cryptorchidism was first described by Bianchi in 1989,⁵⁴ and has since gained wide acceptance.^{55–58} Evidence suggests that most palpable testes can be successfully managed through this incision.^{59,60} According to a recent systematic review that analyzed 1558 scrotal orchidopexies, recurrence of cryptorchidic testes was observed in only 9 cases, testicular hypo/atrophy in 5, and surgical site infections in 13. A secondary inguinal incision was needed in 3.5% of the boys to facilitate high (proximal) testicular dissection. Overall, success rates ranged from 88% to 100%.⁶¹

2.4.2.2 Surgical approach to the non-palpable testis—the role of diagnostic laparoscopy

If the testis is not palpable pre-operatively, as it may occur in up to 20% of UDT cases, examination under anesthesia, an essential step prior to laparoscopic evaluation, can sometimes allow identification of the testis. Otherwise, diagnostic laparoscopy is the procedure of choice in many centres.⁵³ In certain non-palpable testis cases though, palpation of an ipsilateral scrotal nubbin and identification of contralateral compensatory testicular hypertrophy may preclude the need for diagnostic laparoscopy by performing a scrotal incision, which allows removal of the testicular nubbin and confirms the diagnosis of vanishing testis.⁶² If laparoscopy is unavailable, a lengthy inguinal incision extending to the abdominal cavity is sometimes necessary to rule out the presence of an intra-abdominal testis.

When a laparoscopic approach is chosen, three ports are needed: a 3- or 5-mm umbilical trocar for the camera and two 3-mm ports for the working instruments. The position of the trocars on the abdominal wall for both right and left laparoscopic orchidopexies is illustrated in **Figures 2-4A** and **2-4B**.



There are three distinct possible findings and courses of action when diagnostic laparoscopy is used to assess a non-palpable testis:

- 1. Blind-ending vessels, indicating a vanishing intra-abdominal testis (**Figure 2-5**); no further exploration is necessary (10%).
- 2. Spermatic cord structures entering the inguinal canal (Figure 2-6) through the internal inguinal ring (34%). Inguinal exploration may find an atrophic testis (nubbin), which may or may not be removed, or a healthy testis amenable to standard orchidopexy.
- **3.** Intra-abdominal (37%; **Figure 2-7**) or peeping testis (11%), which will require either an open or a laparoscopic approach.⁶³

FIGURE 2-5

Laparoscopic view of a vanishing intra-abdominal testis with blind-ending testicular vessels and vas.



FIGURE 2-6

Laparoscopic view of testicular vessels and vas deferens entering the internal inguinal ring.



FIGURE 2-7 Laparoscopic view of an intra-abdominal testis.



2.4.2.3 Inguinal approach to the high inguinal, canalicular, or intra-abdominal testis

Bringing a high testicle down to the scrotum while preserving its blood supply can sometimes be a surgical challenge. Helpful maneuvers include division of the lateral fibrous attachments of the cord at the internal inguinal ring, blunt dissection of the retroperitoneal spermatic vessels (which are usually the limiting factor) up to the lower pole of the kidney, and mobilization of the cord medial to the inferior epigastric vessels (Prentiss maneuver). Despite these steps, if the testis still does not reach the scrotum, a Fowler-Stephens orchidopexy may be performed.⁶⁴

2.4.2.3.1 Fowler-Stephens orchidopexy

The Fowler-Stephens (FS) technique was originally described as a single-stage open inguinal approach for the intra-abdominal testis in which the testicular artery and veins were too short to allow adequate testicular mobilization into the scrotum through standard orchidopexy.⁶⁵ This operation involves clipping and transection of the testicular vessels with preservation of the collateral arterial flow through the deferential artery and cremasteric vessels. The risk of this technique resides in failure to develop adequate collateral blood supply by the deferential artery, which may result in testicular atrophy. After ligation of the testicular vessels, vasocongestion may develop, impairing the venous blood return, which may also contribute to testicular atrophy. The presence of a long-looping vas deferens may increase this risk, especially when the procedure is done laparoscopically.⁶⁶ An alternative to the FS technique, which depends on a proximal ligation of the spermatic vessels, is the technique of low spermatic vessel ligation described by Koff and Sethi.⁶⁷ Testis viability using this method has been reported as 93% at 1 year of follow-up.

The anticipated advantage of a two-stage FS orchidopexy with testicular vessel ligation is two-fold: 1) to allow for development of collateral blood supply to compensate for division of the main blood flow to the testis, and 2) to create greater mobility of the testis with its proper placement into the scrotum. Preservation of the gubernaculum may also decrease the likelihood of testicular atrophy.⁶⁸

The main surgical steps of the standard open FS orchidopexy are briefly described as follows: After opening the external oblique fascia through an inguinal incision, the hernia sac is dissected at the level of the internal inguinal ring without dividing the cremasteric fibres. The distal gubernacular attachments and the collateral vessels on the floor of the inguinal canal are left undisturbed. The medial peritoneal strip between the vas and the testis is carefully preserved. Further mobilization, especially in case of a long loop vas deferens, is preferably done under direct control of a small tunica albuginea incision on the testis to ensure good blood supply before dividing any potential collaterals (Fowler-Stephens test). After ligating and dividing the testicular vessels, the normal pathway of testicular descent through the inguinal canal is maintained, preserving the cremasteric blood supply.⁶⁵

A laparoscopic approach emerged over 20 years ago⁶⁹ and since then has been used to perform either one- or two-stage FS orchidopexy, with high success rates.⁷⁰⁻⁷²

2.4.3 **Orchidopexy success rates**

Success rates of orchidopexy are directly related to the anatomic position of the testis. These rates range from 92% for standard inguinal open orchidopexy for testes located below the external inguinal ring to 67% for one-stage FS orchidopexy for non-palpable testes.⁹

A recent systematic review has compared the success rates for primary orchidopexy, one-, and twostage FS procedures. According to this review, the weighted success rate for all three approaches exceeded 75%. Independently, the overall success rates were 78.7%, 86%, and 96.4% for one-, twostage FS, and primary orchidopexy, respectively.⁷³

2.4.3.1 **Effectiveness of surgical approach (open versus laparoscopic orchidopexy)**

Laparoscopic orchidopexy outcomes are comparable with those of open surgery.^{74,75} Based on a randomized controlled trial that compared outcomes after two-stage laparoscopic FS orchidopexy versus open orchidopexy for non-palpable testes, patients who underwent the laparoscopic approach were noticed to have statistically significantly shorter operative time and return to normal activities. Although all testes in both groups were noted to have satisfactory scrotal position after surgery, 2 (10%) of the 20 testes in the laparoscopic arm and 3 (19%) of the 16 testes in the open arm had atrophied after 1 year of follow-up.⁷⁶

2.5 **Complications**

The most alarming complication of inguinal orchidopexy is testicular atrophy, which occurs when the testicular vessels are damaged. According to a recent systematic review on this topic,⁷³ pooled atrophy rates were 1.83% for primary orchidopexy (range: 0%–4%),^{70,77–80} 28.1% for one-stage FS (range: 22%–67%),^{70,77,78} and 8.2% for two-stage FS (range: 0%–12%).^{70,77–80} Similarly, another study has shown that surgical outcomes for intra-abdominal testes were better with a one-stage orchidopexy preserving the testicular vessels compared with the FS technique.⁸¹

Rare complications include testicular ascent, where the testis gets trapped at the entrance of the scrotum, and vas deferens injury. Other orchidopexy-related complications might include wound infection, dehiscence, and hematoma.

2.6 Suggested Treatment Algorithm

- 1. Bilateral cryptorchidism after 6 months of age:
 - i. rule out retractile testes
 - ii. consider evaluation for disorders of sexual differentiation
- 2. Unilateral palpable UDT: inguinal or scrotal orchidopexy at age 6–12 months
- 3. Unilateral non-palpable or peeping testis:
 - i. proceed to diagnostic laparoscopy, if available:
 - a. if vanishing testis (blind-ending vessels), no further treatment

- **b.** if vessels seen entering internal ring, inguinal exploration with orchidopexy or excision of atrophic testis
- **c**. one- or two-stage laparoscopic FS orchidopexy for intra-abdominal testis
- ii. if laparoscopy not available, inguinal exploration +/- abdominal exploration with primary or staged orchidopexy
- 4. Unilateral UDT after puberty, orchidectomy (see also chapter on Adolescent Urology)

2.7 **Recommendations: Surgical Management of Cryptorchidism**

- Orchidopexy should be performed between 6 and 12 months of age (LOE 2)
- Success rates of testicular descent are directly related to the anatomic position of the testis. These rates range from 92% for standard inguinal open orchidopexy for testes located below the external inguinal ring to 67% for one-stage FS orchidopexy for non-palpable testes (LOE 3)
- Most palpable testes can be successfully managed through a scrotal approach, with success rates ranging from 88% to 100% (LOE 3)
- Results of open versus laparoscopic orchidopexy (primary or staged) are fairly comparable; however, laparoscopy provides significantly less morbidity (poor quality randomized controlled trial; LOE 2)
- Atrophy rates ranged from 0% to 4% for primary orchidopexy, 22% to 67% for onestage FS, and 0% to 12% for two-stage FS (LOE 3)

2.8 Cryptorchidism and Malignancy

The baseline age-adjusted risk of testicular cancer is 5.5 per 100,000.⁸² The cause of testicular cancer is unknown and likely multifactorial. Evidence suggests that both genetic and environmental factors play a role in the development of testicular cancer.⁸³ Cryptorchidism is a known risk factor for testicular cancer, and the risk of testicular cancer is 2 to 8 times higher in men with a history of cryptor-chidism compared with the general population.^{84,85}

Not only is cryptorchidism associated with an increased risk of testicular cancer, but also the age at which orchidopexy occurs influences this risk. A Swedish study by Pettersson and colleagues demonstrated that boys who underwent later orchidopexy (after age 12 years) were two-fold more likely to develop testicular cancer in the affected testis compared with those who had surgery prior to age 13 years.⁸⁵ However, regardless of the age at which orchidopexy was performed, the risk of testicular cancer in men with history of cryptorchidism remained elevated above the general population. While orchidopexy prior to puberty is associated with a lower risk of malignancy in the ipsilateral testis, the optimal age at which orchidopexy should occur in order to provide the lowest risk for malignancy has not been determined. Moreover, the risk of testicular cancer in unilateral UDT may not be limited to the ipsilateral testis. Meta-analytic data of 199 testicular tumors in men with unilateral cryptorchidism demonstrated that the risk of testicular cancer is increased in both testes, though to a much greater degree in the ipsilateral side.⁸⁶ These data support that there may be an underlying intrinsic abnormality associated with maldescent affecting both testes. However, there is also evidence that the descended contralateral testis is not at increased risk for malignancy.⁸⁷

The increased risk of testicular cancer in males with a history of cryptorchidism underscores the need for surveillance in this population. To facilitate early detection of testicular cancer, males who have had an orchidopexy should continue to have testicular examination by their primary care providers at their yearly well-child visits and upon puberty, they should begin monthly testicular self-examination.⁸⁸

2.9 **Cryptorchidism and Fertility**

Cryptorchidism is associated with impaired fertility, which is most likely due to a combination of factors, including germ cell loss, faulty germ cell maturation, Leydig cell depletion, and/or testicular fibrosis.^{89,90} Men with a history of bilateral cryptorchidism have decreased paternity rates.^{91,92} Most evidence indicates that paternity is not reduced among those with unilateral cryptorchidism corrected during childhood.⁹³ However, one study suggests that there may be a threshold of germ cell depletion on testis biopsy at the time of unilateral orchidopexy that, once crossed, correlates with later abnormal semen parameters and infertility.⁹⁴

Numerous studies provide evidence of subfertility with unilateral cryptorchidism. The degree of impaired fertility is influenced by the age at which surgical intervention for the undescended testis occurs.⁹⁵ Coughlin *et al.* demonstrated that men who underwent orchidopexy by age two had higher inhibin-B and lower FSH levels compared with those who underwent surgery at a later age, suggesting an overall benefit to earlier orchidopexy.⁹⁶ Moreover, Tasian and colleagues demonstrated an association between testes that remain undescended and an increase in loss of germ cells and Leydig cells, indicating that timely orchidopexy is an important factor for preservation of fertility.⁹⁷ The authors also determined that the risk of germ cell loss is significantly higher in non-palpable testes. McAleer and colleagues found that fertility indices were significantly decreased from normal expected values for all age groups undergoing orchidopexy except for boys aged 1 year or younger.⁹⁸ In addition, fertility parameters, such as mean tubular fertility index and germ cell count per tubule, have been shown to be significantly better in children who undergo surgery for cryptorchidism at age 1 year or younger.⁹⁹ In summary, boys with cryptorchidism, especially those with non-palpable and bilateral undescended testes, may experience impaired fertility as an adult. Therefore, early surgical correction of cryptorchidism is recommended before age 12 months.

2.10 **Recommendations Regarding Malignancy and Fertility for Cryptorchidism**

- Men with a history of cryptorchidism have an increased risk of testicular cancer, and the age at orchidopexy influences the risk of cancer (LOE 2)
- Unilateral maldescent is associated with an increased risk of cancer in the affected testes (LOE 2 and 3)
- Cryptorchidism is associated with impaired fertility; however, paternity is not affected in patients with unilateral cryptorchidism (LOE 3)
- Age of intervention for cryptorchidism influences the degree of impaired fertility (LOE 3)

2.11 Hernia and Hydrocele

2.11.1 **Definition**

Direct inguinal hernias are infrequent in children.¹⁰⁰ More common are indirect hernias, which occur secondary to a patent processus vaginalis that allows for abdominal contents to herniate through the internal ring within the patent processus vaginalis. With a large opening, intestine may pass through the internal ring, generating an indirect hernia. A communicating hydrocele occurs when the channel through the internal ring is small, permitting only peritoneal fluid to get through, rather than abdominal contents. It is important to distinguish between hernias, communicating hydroceles, and non-communicating hydroceles due to their differences. A communicating hydrocele is essentially the same entity as an indirect hernia and different from a non-communicating hydrocele. It is important to distinguish between an indirect hernia, a communicating hydrocele, and non-communicating hydrocele is essentially hydrocele due to their differences in surgical management, including timing of surgery and approach (see section below on treatment of hernias and hydroceles).

2.11.2 Epidemiology

Up to 3% of term infants have an indirect hernia or communicating hydrocele, and this increases by three-fold in premature infants.¹⁰¹ They are more common in males compared with females (5:1) and are located on the right in 59%, on the left in 29%, and bilateral in 12% of cases.¹⁰⁰ Various conditions predispose children to indirect hernias/hydroceles including cystic fibrosis, Ehlers-Danlos syndrome, ventricular-peritoneal shunting, and peritoneal dialysis.¹⁰²⁻¹⁰⁵

2.11.3 **Diagnosis and evaluation**

A hydrocele is a collection of fluid around the testicle within the tunica vaginalis. By history, communicating hydroceles typically fluctuate in size throughout the day as fluid goes back and forth from the abdomen into the scrotum. This collection of fluid can be felt on examination and often compressed back into the abdomen. At times the fluid cannot be compressed into the abdomen, and tense distention can be felt along the cord.

Inguinal hernias are often noted as an intermittent, painless bulge in the groin, scrotum, or labia majora by the parents or the patient. The bulge may be exacerbated by any activity that increases intra-abdominal pressure, such as crying or straining to have a bowel movement. Often a hernia is not associated with pain; however, there may be discomfort, nausea, and vomiting if incarceration occurs and severe pain, nausea, and vomiting with strangulation. Incarceration is more common in infants (30%) compared with older children.¹⁰⁶

On examination, the clinician should try to palpate the bulge at the level of the internal ring and along the inguinal canal. Asking the patient to increase intra-abdominal pressure with a cough or valsalva can be helpful. However, occasionally these maneuvers will not reproduce the bulge of the hernia. If this is the case, history of an intermittent bulge is sufficient evidence for elective surgical exploration. If a bulge is palpated and freely moves in and out of the inguinal canal or if an incarcerated hernia is successfully and easily reduced, an elective hernia repair should be scheduled in the next 1 to 2 weeks.¹⁰⁷ If the hernia is not reducible or if there are signs of a strangulated hernia such as fever, tachycardia, leukocytosis, emesis, severe pain, and erythema to the affected area, then emergent surgery is critical.¹⁰¹

For the majority of patients, history and physical will be sufficient to discern between a hernia versus a hydrocele. Ultrasound can be used to help differentiate between the two entities and may also be useful in the setting of a large hydrocele that inhibits the ability to palpate the testicle. However, it is important to emphasize that ultrasound may fail to detect herniated bowel or falsely identify bowel when only a hydrocele is present.¹⁰⁸ Accordingly, clinical judgment should override imaging findings that are incongruent with patient history and clinical examination.

2.11.4 Surgical treatment

2.11.4.1 **Overview**

Communicating hydroceles and hernias have the same origin: a patent processes vaginalis. The processes vaginalis is a continuation of the peritoneum through the inguinal ring. A hydrocele occurs when peritoneal fluid flows through the processes vaginalis to the inguinal canal or scrotum. A hernia occurs when abdominal contents (usually bowel or omental fat) extend through the the open channel into the inguinal canal or beyond. A hernia can become incarcerated when its contents, (especially bowel) become trapped, or ischemic (strangled).

2.11.4.2 Indication for surgery

2.11.4.2.1 Hernia

Surgical correction (herniorrhaphy) is indicated when signs and symptoms demonstrate a hernia. Incarceration of a hernia is the main complication and danger of a hernia in a child and occurs in around 12% of all children, mainly in the neonatal period. Seventy percent of incarceration occurs in the first year of life.¹⁰⁹ Signs of an incarcerated, strangulated hernia include erythema and hardness in the inguinal region, pain, fever, and other sequelae of ischemic viscera. Because of the potential for incarceration and strangulation and because the probability of spontaneous resolution is low, conservative management is only justified in complex situations, as in premature newborns or children with other severe diseases (and anesthesia risks).^{110,111} In the event of incarceration, manual reduction of the hernia should be attempted in order to allow elective surgery, at which point edema may be less. The incidence of complications, such as testis atrophy and recurrence, are higher in surgery for incarcerated hernias.

2.11.4.2.2 Hydrocele

A small patent processus vaginalis has a high tendency for spontaneous closure in the first year of life, which may be due to the low pressure in the processus and at the internal ring in a non-ambulatory child. As soon as the child starts to walk, the pressure on the internal ring increases, and therefore the probability of spontaneous resolution decreases. Although there are differences in management strategies, one commonly accepted indication for surgical correction is a hydrocele in a child who has started to walk.^{112,113}

2.11.4.2.3 Clinical bilateral hernia

If a hernia is clinically present on both sides, a bilateral surgical correction should be performed during a single procedure.

2.11.4.2.4 Exploring the contralateral side

It is controversial if the contralateral side should be explored in a clinical unilateral hernia. In Europe, only the clinical proven site is corrected, whereas in the United States the practice to explore the contralateral site is more variable.^{114,115} Means of exploration of the contralateral side include herniorraphy, open exploration, and insufflation/laparoscopy.

Considerations that influence whether the contralateral site should be explored are:

- The occurrence of a clinical contralateral hernia after unilateral surgical correction is between 10% and 20%.¹¹⁵
- 2. If exploration of the contralateral site are performed, it is found that about 50% is still patent.¹¹⁵ This is significantly higher than the clinical occurrence and implies that a patent processus vaginalis does not mean that a hernia will develop.
- **3**. Female sex is not associated with a higher probability of development of a contralateral hernia.^{100,116}
- 4. The probability for patent processus on the contralateral side is higher in a premature infant as are the risks of anesthesia; therefore, some experts recommend exploration of the contralateral side in a premature infant with a unilateral hernia.
- Increased abdominal fluid secondary to ascites, ventriculoperitoneal shunt or peritoneal dialysis can influence the development of a symptomatic hernia or hydrocele.

2.11.4.3 **Preparation for surgery**

Surgery for hernia repair or hydrocele correction should preferably be performed as an elective and ambulatory procedure.

2.11.4.4 **Surgical technique**

2.11.4.4.1 Male hernia

A 2- to 3-cm incision is performed in a horizontal skin crease of the lower abdomen. At the level of the symphysis, the spermatic cord is blunt dissected from the surrounding muscular tissue and aponeurosis. It is very important to remove all cremasteric fibres, as this could cause secondary ascending cryptorchidism.¹¹⁷

The processus vaginalis is situated on the anteromedial aspect of the spermatic cord and is identified as a white and shiny structure.

At this stage, the processus vaginalis should be dissected off the vessels and vas deferens up to the internal inguinal canal. It is not necessary to attempt to ligate the processus vaginalis as proximal as possible because the processus, as an outline of the peritoneum, will retract by itself under the abdominal muscles.

In children, it is not necessary to suture any muscle tissue, and it is not necessary to attempt to narrow down the internal ring.

2.11.4.4.2 Male hydrocele

The same surgical steps as previously described for a hernia repair should be taken. The gubernacular attachment is maintained and in this manner the testis may be pulled back down into the scrotum without the need for orchidopexy.

2.11.4.4.3 Female hernia

The procedure in girls is the same as in boys. If a gonadal structure is found within the hernia sac in a phenotypic girl, one should think about testicular feminization, which occurs in about 1% of all girls with a hernia.^{118,119}

2.11.4.5 **Special intra-operative findings**

Ectopic adrenal tissue: 1- to 4-mm structures in the spermatic cord with a typical yellow (adrenal) color can be found in approximately 1% of the patients with a patent processus vaginalis. The origin is found in the early common embryologic origin of the gonadal and adrenal structures. It has no clinical relevance or importance.¹²⁰

Absent vas deferens: this can be found in patients with mucoviscidosis (cystic fibrosis),¹²¹ renal agenesis,¹²² or a congenital measles infection. These patients should be investigated further with a sweat test and a renal ultrasound.
2.11.4.6 **Complications and outcomes**

Injury to the vas deferens: crushing or transsection of the vas deferens is a recognized complication that occurs in less than 1% of hernia/hydrocele repairs. Vas injury can result in occlusion of the vas deferens. Should this injury occur, the parents should be informed. It is not recommended to perform a vasovasostomy in a prepubertal child. The success rate of reconstruction later in the adult life has a limited success rate of 20% to 30%.^{123,124}

Testicular atrophy: the incidence is about 0.2% to 0.6% and is higher if the hernia is associated with an undescended testis.¹²⁵ Testicular atrophy is most frequently the consequence of an incarceration and occurs in these situations in about 7%.¹²⁶ Injury to the spermatic vessels can and should be prevented in elective situations.

Post-operative testicular "ascent": this complication occurs in about 0.8% to 2%.¹¹⁷ The most frequent causes for this complication is that either insufficient dissection of the cremasteric fibres was performed or that the testis was pulled into the groin during the surgery and not be pulled back again toward the scrotum at the end of the surgery.

Recurrence occurs in about 0.5% to 2.5% and increases up to 6% if the surgery was performed for incarceration.¹²⁶ The most frequent causes are either incomplete transection of the cremasteric fibers or failure to replace the testicle into the scrotum prior to closure of the incision. It is therefore recommended to attempt to manually reduce the hernia and then perform elective surgery after some time has passed to allow inflammation to decrease.

2.11.5 **Recommendations on hernia and hydrocele**

The indication for surgery of a hernia exists, regardless of age, when clinical signs and symptoms are present. In the event of a hydrocele (small patent processus vaginalis), there is a high tendency for spontaneous resolution in the first year of life (LOE 3)

In the event of incarceration, manual reduction of the hernia should be attempted to allow elective surgery. The incidence of complications is higher during surgery for incarcerated hernias (LOE 3)

Routine contralateral groin exploration for hernia is not indicated for either boys or girls (LOE 3)



2.12 References

- 1. Sijstermans K, Hack WW, Meijer RW, *et al.* The frequency of undescended testis from birth to adulthood: a review. Int J Androl. 2008;31(1):1–11.
- 2. Berkowitz GS, Lapinski RH, Dolgin SE, et al. Prevalence and natural history of cryptorchidism. Pediatrics. 1993;92(1):44-49.
- Hack WW, van der Voort-Doedens LM, Goede J, et al. Natural history and long-term testicular growth of acquired undescended testis after spontaneous descent or pubertal orchidopexy. BJU Int. 2010;106(7):1052–1059.
- Elert A, Jahn K, Heidenreich A, et al. Population-based investigation of familial undescended testis and its association with other urogenital anomalies. J Pediatr Urol. 2005;1(6):403–407.
- Schnack TH, Zdravkovic S, Myrup C, et al. Familial aggregation of cryptorchidism--a nationwide cohort study. Am J Epidemiol. 2008;167(12):1453–1457.
- Main KM, Skakkebaek NE, Toppari J. Cryptorchidism as part of the testicular dysgenesis syndrome: the environmental connection. Endocr Dev. 2009;14:167–173.
- Snodgrass W, Bush N, Holzer M, et al. Current referral patterns and means to improve accuracy in diagnosis of undescended testis. Pediatrics. 2011;127(2):e382–e388.
- Cendron M, Huff DS, Keating MA, et al. Anatomical, morphological and volumetric analysis: a review of 759 cases of testicular maldescent. J Urol. 1993;149(3):570–573.
- 9. Docimo SG. The results of surgical therapy for cryptorchidism: a literature review and analysis. J Urol. 1995;154(3):1148–1152.
- Hurwitz RS, Kaptein JS. How well does contralateral testis hypertrophy predict the absence of the nonpalpable testis? J Urol. 2001;165(2):588–592.
- 11. White PC. Neonatal screening for congenital adrenal hyperplasia. Nat Rev Endocrinol. 2009;5(9):490-498.
- 12. Cox MJ, Coplen DE, Austin PF. The incidence of disorders of sexual differentiation and chromosomal abnormalities of cryptorchidism and hypospadias stratified by meatal location. J Urol. 2008;180(6):2649–2652; discussion 2652.
- Tasian GE, Copp HL. Diagnostic performance of ultrasound in nonpalpable cryptorchidism: a systematic review and meta-analysis. Pediatrics. 2011;127(1):119–128.
- Tasian GE, Copp HL, Baskin LS. Diagnostic imaging in cryptorchidism: utility, indications, and effectiveness. J Pediatr Surg. 2011;46(12):2406–2413.
- Kubota Y, Temelcos C, Bathgate RA, et al. The role of insulin 3, testosterone, Mullerian inhibiting substance and relaxin in rat gubernacular growth. Mol Hum Reprod. 2002;8(10):900–905.
- Hutson JM, Baker M, Terada M, Zet al. Hormonal control of testicular descent and the cause of cryptorchidism. Reprod Fertil Dev. 1994;6(2):151–156.
- Rohatgi M, Menon PS, Verma IC, et al. The presence of intersexuality in patients with advanced hypospadias and undescended gonads. J Urol. 1987;137(2):263–267.
- Kolon TF, Miller OF. Comparison of single versus multiple dose regimens for the human chorionic gonadotropin stimulatory test. J Urol. 2001;166(4):1451–1454.
- Davenport M, Brain C, Vandenberg C, et al. The use of the hCG stimulation test in the endocrine evaluation of cryptorchidism. Br J Urol. 1995;76(6):790–794.
- De Rosa M, Lupoli G, Mennitti M, et al. Congenital bilateral anorchia: clinical, hormonal and imaging study in 12 cases. Andrologia. 1996;28(5):281–285.
- Thorup J, Petersen BL, Kvist K, *et al.* Bilateral vanished testes diagnosed with a single blood sample showing very high gonadotropins (follicle-stimulating hormone and luteinizing hormone) and very low inhibin B. Scand J Urol Nephrol. 2011;45(6):425-431.
- Aycan Z, Ustunsalih-Inan Y, Cetinkaya E, et al. Evaluation of low-dose hCG treatment for cryptorchidism. Turk J Pediatr. 2006;48(3):228–231.

- Bica DT, Hadziselimovic F. Buserelin treatment of cryptorchidism: a randomized, double-blind, placebo-controlled study. J Urol. 1992;148(2 Pt 2):617–621.
- Christiansen P, Muller J, Buhl S, *et al.* Treatment of cryptorchidism with human chorionic gonadotropin or gonadotropin releasing hormone. A double-blind controlled study of 243 boys. Horm Res. 1988;30(4-5):187–192.
- 25. Esposito C, De Lucia A, Palmieri A, *et al.* Comparison of five different hormonal treatment protocols for children with cryptorchidism. Scand J Urol Nephrol. 2003;37(3):246–249.
- Forest MG, Lecoq A, David M, et al. Effects of human chorionic gonadotropin, androgens, adrenocorticotropin hormone, dexamethasone and hyperprolactinemia on plasma sex steroid-binding protein. Ann N Y Acad Sci. 1988;538:214–234.
- Hesse V, Fischer G. Three injections of human chorionic gonadotropin are as effective as ten injections in the treatment of cryptorchidism. Horm Res. 1988;30(4-5):193–197.
- 28. Rajfer J, Handelsman DJ, Swerdloff RS, *et al.* Hormonal therapy of cryptorchidism. A randomized, double-blind study comparing human chorionic gonadotropin and gonadotropin-releasing hormone. N Engl J Med. 1986;314(8):466-470.
- De Muinck Keizer-Schrama SM, Hazebroek FW, Drop SL, et al. LH-RH nasal spray treatment for cryptorchidism. A double-blind, placebo-controlled study. Eur J Pediatr. 1987;146(suppl 2):S35–S37.
- Hagberg S, Westphal O. Treatment of undescended testes with intranasal application of synthetic LH-RH. Eur J Pediatr. 1982;139(4):285–288.
- Hazebroek FW, de Muinck Keizer-Schrama SM, van Maarschalkerweerd M, et al. Why luteinizing-hormone-releasing-hormone nasal spray will not replace orchiopexy in the treatment of boys with undescended testes. J Pediatr Surg. 1987;22(12):1177–1182.
- 32. Karpe B, Eneroth P, Ritzen EM. LHRH treatment in unilateral cryptorchidism: effect on testicular descent and hormonal response. J Pediatr. 1983;103(6):892–897.
- Olsen LH, Genster HG, Mosegaard A, et al. Management of the non-descended testis: doubtful value of luteinizing-hormonereleasing-hormone (LHRH). A double-blind, placebo-controlled multicentre study. Int J Androl. 1992;15(2):135–143.
- Wit JM, Delemarre-Van de Waal HA, Bax NM, et al. Effect of LHRH treatment on testicular descent and hormonal response in cryptorchidism. Clin Endocrinol (0xf). 1986;24(5):539–548.
- Hadziselimovic F, Herzog B. Treatment with a luteinizing hormone-releasing hormone analogue after successful orchiopexy markedly improves the chance of fertility later in life. J Urol. 1997;158(3 Pt 2):1193–1195.
- Bertelloni S, Baroncelli GI, Ghirri P, et al. Hormonal treatment for unilateral inguinal testis: comparison of four different treatments. Horm Res. 2001;55(5):236–239.
- 37. Forest MG, David M, David L, *et al.* Undescended testis: comparison of two protocols of treatment with human chorionic gonadotropin. Effect on testicular descent and hormonal response. Horm Res. 1988;30(4-5):198-205; discussion 205–206.
- Garagorri JM, Job JC, Canlorbe P, et al. Results of early treatment of cryptorchidism with human chorionic gonadotropin. J Pediatr. 1982;101(6):923–927.
- Job JC, Canlorbe P, Garagorri JM, et al. Hormonal therapy of cryptorchidism with human chorionic gonadotropin (HCG). Urol Clin North Am. 1982;9(3):405–411.
- Waldschmidt J, Doede T, Vygen I. The results of 9 years of experience with a combined treatment with LH-RH and HCG for cryptorchidism. Eur J Pediatr. 1993;152(suppl 2):S34–S36.
- 41. Lala R, Matarazzo P, Chiabotto P, *et al.* Combined therapy with LHRH and HCG in cryptorchid infants. Eur J Pediatr. 1993;152(suppl 2):S31–S33.
- De Muinck Keizer-Schrama SM, Hazebroek FW, Matroos AW, et al. Double-blind, placebo-controlled study of luteinisinghormone-releasing-hormone nasal spray in treatment of undescended testes. Lancet. 1986;1(8486):876–880.
- Hadziselimovic F, Girard J, Herzog B. [4 years' experience with combined hormonal treatment of cryptorchism]. Z Kinderchir. 1984;39(5):324–327.
- 44. Huff DS, Snyder HM, 3rd, Rusnack SL, et al. Hormonal therapy for the subfertility of cryptorchidism. Horm Res. 2001;55(1):38-40.
- 45. Jallouli M, Rebai T, Abid N, et al. Neoadjuvant gonadotropin-releasing hormone therapy before surgery and effect on fertility index in unilateral undescended testes: a prospective randomized trial. Urology. 2009;73(6):1251–1254.

- Zivkovic D, Bica DG, Hadziselimovic F. Effects of hormonal treatment on the contralateral descended testis in unilateral cryptorchidism. J Pediatr Urol. 2006;2(5):468–472.
- 47. Dunkel L, Taskinen S, Hovatta O, *et al.* Germ cell apoptosis after treatment of cryptorchidism with human chorionic gonadotropin is associated with impaired reproductive function in the adult. J Clin Invest. 1997;100(9):2341–2346.
- Hadziselimovic F, Huff D, Duckett J, et al. Long-term effect of luteinizing hormone-releasing hormone analogue (buserelin) on cryptorchid testes. J Urol. 1987;138(4 Pt 2):1043–1045.
- 49. Timing of elective surgery on the genitalia of male children with particular reference to the risks, benefits, and psychological effects of surgery and anesthesia. American Academy of Pediatrics. Pediatrics 1996;97(4):590–594.
- 50. Hutson JM, Li R, Southwell BR, *et al.* Germ cell development in the postnatal testis: the key to prevent malignancy in cryptorchidism? Front Endocrinol (Lausanne). 2013;3:176.
- Kollin C, Karpe B, Hesser U, et al. Surgical treatment of unilaterally undescended testes: testicular growth after randomization to orchiopexy at age 9 months or 3 years. J Urol. 2007;178(4 Pt 2):1589–1593; discussion 1593.
- Wenzler DL, Bloom DA, Park JM. What is the rate of spontaneous testicular descent in infants with cryptorchidism? J Urol. 2004;171(2 Pt 1):849–851.
- 53. Wein AJ, Kavoussi LR, Novick AC, et al. Campbell-Walsh Urology. 10th ed. Philadelphia, W.B. Saunders, 2007.
- 54. Bianchi A, Squire BR. Transscrotal orchidopexy: orchidopexy revised. Pediatric Surg Int. 1989;4(3):189–192.
- 55. Al-Mandil M, Khoury AE, El-Hout Y, et al. Potential complications with the prescrotal approach for the palpable undescended testis? A comparison of single prescrotal incision to the traditional inguinal approach. J Urol. 2008;180(2):686–689.
- Callewaert PR, Rahnama'i MS, Biallosterski BT, et al. Scrotal approach to both palpable and impalpable undescended testes: should it become our first choice? Urology. 2010;76(1):73–76.
- 57. Gordon M, Cervellione RM, Morabito A, *et al.* 20 years of transcrotal orchidopexy for undescended testis: results and outcomes. J Pediatr Urol. 2010;6(5):506–512.
- Yucel S, Celik O, Kol A, et al. Initial pre-scrotal approach for palpable cryptorchid testis: results during a 3-year period. J Urol. 2011;185(2):669–672.
- Bassel YS, Scherz HC, Kirsch AJ. Scrotal incision orchiopexy for undescended testes with or without a patent processus vaginalis. J Urol. 2007;177(4):1516–1518.
- Cloutier J, Moore K, Nadeau G, et al. Modified scrotal (Bianchi) mid raphe single incision orchiopexy for low palpable undescended testis: early outcomes. J Urol. 2011;185(3):1088–1092.
- 61. Novaes HF, Carneiro Neto JA, Macedo A, *et al.* Single scrotal incision orchiopexy a systematic review. Int Braz J Urol. 2013;39(3):305–311.
- 62. Snodgrass WT, Yucel S, Ziada A. Scrotal exploration for unilateral nonpalpable testis. J Urol. 2007;178(4 Pt 2):1718–1721.
- Cisek LJ, Peters CA, Atala A, et al. Current findings in diagnostic laparoscopic evaluation of the nonpalpable testis. J Urol. 1998;160(3 Pt 2):1145–1149; discussion 1150.
- Kirsch AJ, Escala J, Duckett JW, et al. Surgical management of the nonpalpable testis: the Children's Hospital of Philadelphia experience. J Urol. 1998;159(4):1340–1343.
- Fowler R, Stephens FD. The role of testicular vascular anatomy in the salvage of high undescended testes. Aust N Z J Surg. 1959;29:92–106.
- Dave S, Manaboriboon N, Braga LH, et al. Open versus laparoscopic staged Fowler-Stephens orchiopexy: impact of long loop vas. J Urol. 2009;182(5):2435–2439.
- Koff SA, Sethi PS. Treatment of high undescended testes by low spermatic vessel ligation: an alternative to the Fowler-Stephens technique. J Urol. 1996;156(2 Pt 2):799-803; discussion 803.
- Braga LH, DeMaria J. Laparascopic orchidopexy preserving the cremasteric vessels and using the inguinal canal as a pathway for testicular descent. Can Urol Assoc J. 2009;3(3):S60.
- 69. Caldamone AA, Amaral JF. Laparoscopic stage 2 Fowler-Stephens orchiopexy. J Urol. 1994;152(4):1253–1256.

- 70. Baker LA, Docimo SG, Surer I, et al. A multi-institutional analysis of laparoscopic orchidopexy. BJU Int. 2001;87(6):484-489.
- 71. Chang B, Palmer LS, Franco I. Laparoscopic orchidopexy: a review of a large clinical series. BJU Int. 2001;87(6):490-493.
- 72. Chang M, Franco I. Laparoscopic Fowler-Stephens orchiopexy: the Westchester Medical Center experience. J Endourol. 2008;22(6):1315–1319.
- Penson D, Krishnaswami S, Jules A, et al. Effectiveness of hormonal and surgical therapies for cryptorchidism: a systematic review. Pediatrics. 2013;131(6):e1897–e1907.
- 74. Chandrasekharam VV. Laparoscopy vs inguinal exploration for nonpalpable undescended testis. Indian J Pediatr. 2005;72(12):1021–1023.
- Ferro F, Spagnoli A, Zaccara A, et al. Is preoperative laparoscopy useful for impalpable testis? J Urol. 1999;162(3 Pt 2):995–996; discussion 997.
- 76. Abolyosr A. Laparoscopic versus open orchiopexy in the management of abdominal testis: a descriptive study. Int J Urol. 2006;13(11):1421–1424.
- Denes FT, Saito FJ, Silva FA, et al. Laparoscopic diagnosis and treatment of nonpalpable testis. Int Braz J Urol. 2008;34(3):329– 334; discussion 335.
- Humphrey GM, Najmaldin AS, Thomas DF. Laparoscopy in the management of the impalpable undescended testis. Br J Surg. 1998;85(7):983–985.
- 79. Moursy EE, Gamal W, Hussein MM. Laparoscopic orchiopexy for non-palpable testes: outcome of two techniques. J Pediatr Urol. 2011;7(2):178–181.
- Radmayr C, Oswald J, Schwentner C, et al. Long-term outcome of laparoscopically managed nonpalpable testes. J Urol. 2003;170(6 Pt 1):2409–2411.
- Stec AA, Tanaka ST, Adams MC, et al. Orchiopexy for intra-abdominal testes: factors predicting success. J Urol. 2009;182(4 Suppl):1917–1920.
- National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Statistics. 2014. Available: http://seer. cancer.gov/statfacts/html/testis.html; Accessed: August 10, 2013.
- McIntyre A, Gilbert D, Goddard N, et al. Genes, chromosomes and the development of testicular germ cell tumors of adolescents and adults. Genes Chromosomes Cancer. 2008;47(7):547–557.
- 84. Dieckmann KP, Pichlmeier U. Clinical epidemiology of testicular germ cell tumors. World J Urol. 2004;22(1):2–14.
- Pettersson A, Richiardi L, Nordenskjold A, et al. Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med. 2007;356(18):1835–1841.
- Akre O, Pettersson A, Richiardi L. Risk of contralateral testicular cancer among men with unilaterally undescended testis: a meta analysis. Int J Cancer. 2009;124(3):687–689.
- 87. Wood HM, Elder JS. Cryptorchidism and testicular cancer: separating fact from fiction. J Urol. 2009;181(2):452-461.
- Urology Care Foundation. Urology A Z. Testicular Self-Examination (TSE). 2011. Available: http://www.urologyhealth.org/ urology/index.cfm?article=101&display=1; Accessed: August 10, 2013.
- Hadziselimovic F, Herzog B. The importance of both an early orchidopexy and germ cell maturation for fertility. Lancet. 2001;358(9288):1156–1157.
- 90. Trussell JC, Lee PA. The relationship of cryptorchidism to fertility. Curr Urol Rep. 2004;5(2):142-148.
- Engeler DS, Hosli PO, John H, et al. Early orchiopexy: prepubertal intratubular germ cell neoplasia and fertility outcome. Urology. 2000;56(1):144–148.
- Lee PA, O'Leary LA, Songer NJ, et al. Paternity after bilateral cryptorchidism. A controlled study. Arch Pediatr Adolesc Med. 1997;151(3):260–263.
- Lee PA, Coughlin MT. The single testis: paternity after presentation as unilateral cryptorchidism. J Urol. 2002;168(4 Pt 2):1680-1682; discussion 1682–1683.

- Cortes D, Thorup JM, Lindenberg S. Fertility potential after unilateral orchiopexy: an age independent risk of subsequent infertility when biopsies at surgery lack germ cells. J Urol. 1996;156(1):217–220.
- Cortes D, Thorup JM, Visfeldt J. Cryptorchidism: aspects of fertility and neoplasms. A study including data of 1,335 consecutive boys who underwent testicular biopsy simultaneously with surgery for cryptorchidism. Horm Res. 2001;55(1):21–27.
- Coughlin MT, Bellinger MF, Lee PA. Age at unilateral orchiopexy: effect on hormone levels and sperm count in adulthood. J Urol. 1999;162(3 Pt 2):986–988; discussion 989.
- Tasian GE, Hittelman AB, Kim GE, et al. Age at orchiopexy and testis palpability predict germ and Leydig cell loss: clinical predictors of adverse histological features of cryptorchidism. J Urol. 2009;182(2):704–709.
- 98. McAleer IM, Packer MG, Kaplan GW, et al. Fertility index analysis in cryptorchidism. J Urol. 1995;153(4):1255–1258.
- Park KH, Lee JH, Han JJ, et al. Histological evidences suggest recommending orchiopexy within the first year of life for children with unilateral inguinal cryptorchid testis. Int J Urol. 2007;14(7):616–621.
- Ein SH, Njere I, Ein A. Six thousand three hundred sixty-one pediatric inguinal hernias: a 35-year review. J Pediatr Surg. 2006;41(5):980–986.
- Lao OB, Fitzgibbons RJ, Jr., Cusick RA. Pediatric inguinal hernias, hydroceles, and undescended testicles. Surg Clin North Am. 2012;92(3):487–504, vii.
- Chen YC, Wu JC, Liu L, et al. Correlation between ventriculoperitoneal shunts and inguinal hernias in children: an 8-year follow-up. Pediatrics. 2011;128(1):e121–e126.
- Holsclaw DS, Shwachman H. Increased incidence of inguinal hernia, hydrocele, and undescended testicle in males with cystic fibrosis. Pediatrics. 1971;48(3):442–445.
- 104. Khoury AE, Charendoff J, Balfe JW, et al. Hernias associated with CAPD in children. Adv Perit Dial. 1991;7:279–282.
- Liem MS, van der Graaf Y, Beemer FA, et al. Increased risk for inguinal hernia in patients with Ehlers-Danlos syndrome. Surgery. 1997;122(1):114–115.
- 106. Cates M, Billmire DF, Bull MJ, et al. Gastroesophageal dysfunction in Cornelia de Lange syndrome. J Pediatr Surg. 1989;24(3):248-250.
- 107. Stylianos S. Commentary: the role of sonography in the initial evaluation of children after blunt abdominal trauma. Pediatr Radiol. 1993;23(3):164.
- 108. van den Berg JC, de Valois JC, Go PM, *et al.* Detection of groin hernia with physical examination, ultrasound, and MRI compared with laparoscopic findings. Invest Radiol. 1999;34(12):739–743.
- Rowe MI, Clatworthy HW. Incarcerated and strangulated hernias in children. A statistical study of high-risk factors. Arch Surg. 1970;101(2):136–139.
- 110. Koop CE. Inguinal herniorrhaphy in infants and children. Surg Clin North Am. 1957;37(6):1675–1682.
- 111. White JJ, Haller JA Jr, Dorst JP. Congenital inguinal hernia and inguinal herniography. Surg Clin North Am. 1970;50(4):823-837.
- 112. Hall NJ, Ron O, Eaton S, et al. Surgery for hydrocele in children-an avoidable excess? J Pediatr Surg. 2011;46(12):2401–2405.
- Koski ME, Makari JH, Adams MC, et al. Infant communicating hydroceles--do they need immediate repair or might some clinically resolve? J Pediatr Surg. 2010;45(3):590–593.
- 114. Kiesewetter WB, Oh KS. Unilateral inguinal hernias in children: What about the opposite side? Arch Surg. 1980;115(12):1443–1445.
- Nataraja RM, Mahomed AA. Systematic review for paediatric metachronous contralateral inguinal hernia: a decreasing concern. Pediatr Surg Int. 2011;27(9):953–961.
- 116. Erdogan D, Karaman I, Aslan MK, *et al.* Analysis of 3776 pediatric inguinal hernia and hydrocele cases in a tertiary center. J Pediatr Surg. 2013;48(8):1767–1772.
- 117. Surana R, Puri P. latrogenic ascent of the testis: an under-recognized complication of inguinal hernia operation in children. Br J Urol 1994;73(5):580–581.
- 118. Kaplan SA, Snyder WH Jr, Little S. Inguinal hernias in females and the testicular feminization syndrome. Am J Dis Child. 1969;117(2):243-251.

- 119. Punnett HH, Kistenmacher ML, Toro-Sola M. Letter: Testicular feminisation and inguinal hernia. Lancet. 1973;2(7833):852.
- 120. Mendez R, Tellado MG, Somoza I, *et al.* Ectopic adrenal tissue in the spermatic cord in pediatric patients: surgical implications. Int Braz J Urol. 2006;32(2):202–207; discussion 207.
- 121. Leonardi S, Bombace V, Rotolo N, *et al.* Congenital absence of vas deferens and cystic fibrosis. Minerva Pediatr. 2003;55(1):43–47, 47–50.
- 122. Lukash F, Zwiren GT, Andrews HG. Significance of absent vas deferens at hernia repair in infants and children. J Pediatr Surg. 1975;10(5):765–769.
- 123. Shandling B, Janik JS. The vulnerability of the vas deferens. J Pediatr Surg. 1981;16(4):461-464.
- 124. Silber SJ. Perfect anatomical reconstruction of vas deferens with a new microscopic surgical technique. Fertil Steril. 1977;28(1):72–77.
- 125. Rosenberg J. Pediatric inguinal hernia repair-a critical appraisal. Hernia. 2008;12(2):113–115.
- 126. Lau ST, Lee YH, Caty MG. Current management of hernias and hydroceles. Semin Pediatr Surg. 2007;16(1):50-57.

Committee



Hypospadias

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3.1 Introduction

Hypospadias is one of the most common malformations of the penis. Depending on the severity of the defect there may be cosmetic, functional and psychological long-term effects for the patient. A collaborative working group consisting of pediatric urologists with an interest in hypospadias gathered under the auspices of Société Internationale d'Urologie in an effort to produce the update of current best practice options for the treatment of hypospadias. The guidelines are based on a systematic review using MEDLINE, between 1990 and 2013.

Whenever possible, statements have been classified in terms of level of evidence (LOE) and grade of recommendation (GOR) as proposed by the Centre For Evidence-Based Medicine.¹ However, due to the limited availability of randomized controlled trials and high-quality studies, this document will largely be a consensus document including expert opinion and common sense. The criteria for the level of evidence and grade of recommendation used are outlined in **Tables 3-1** and **3-2**, respectively.

TABLE 3-1 EVIDENCE LEVELS OF DIFFERENT TYPES OF STUDY1

Level	Study	
1A	Systematic review of randomized controlled trials	
1B	Randomized controlled trial	
2A	Systematic review of cohort studies	
2B	Cohort study (including low quality RCT; e.g. <80% follow-up)	
2C	"Outcomes" research; ecological studies	
ЗA	Systematic review of case-control studies	
3B	Individual case-control study	
4	Case-series (and poor quality cohort and case-control studies)	
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	

TABLE 3-2 GRADES OF RECOMMENDATION¹

А	Consistent level 1 studies	
В	Consistent level 2 or 3 studies or extrapolations from level 1 studies	
С	Level 4 studies or extrapolations from level 2 or 3 studies	
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level	

3.2 Why Should Hypospadias Be Corrected?

The goal of hypospadias repair is re-creation of a functionally and cosmetically normal penis. Penile anatomy and appearance varies widely. However, it is generally accepted that the following should be corrected:

- Penile deviation and rotation (functional and cosmetic)
- Glans tilt (functional)
- Glans cleft (functional and cosmetic)
- Ectopic urethral meatus (functional and cosmetic)
- Meatal stenosis (functional)
- Peno-scrotal transposition cosmetic
- Hooded prepuce (cosmetic)

There should be a good caliber urethra with a slit-like urethral meatus at the tip of the glans, allowing micturition in a single coherent urinary stream. The penis should be straight on erection allowing sexual activity and successful intercourse with pleasure. The penile skin should be appealing with as minimal scarring as possible.

Function, cosmesis, and psychological impact go hand in hand. Patients with severe hypospadias and those with a non-favorable surgical outcome are more likely to suffer a negative psychological impact than those with minor hypospadias and good surgical results. In cases of minor variants of hypospadias, a conservative approach may be considered and not correct the defect.

3.2.1 **Recommendation and level of evidence**

There is a substantial lack of long-term studies showing the effects of hypospadias surgery on cosmetic, functional, and psychological outcome. Therefore, recommendation on indication for hypospadias surgery is largely based on expert opinion and common sense (LOE 3–5, GOR B–D).

3.3 How Should Hypospadias Be Classified?

Traditionally, hypospadias has been classified according to the meatal position (**Figure 3-1**); distal (glandular, coronal, and distal penile) or proximal (proximal penile, peno-scrotal, scrotal or perineal). Despite several limitations, a classification based on the level of urethral orifice is easy to follow and enables communication even among physicians not trained in the repair of hypospadias. However, the mere position of the meatus often is neither sufficient to explain the complex nature of hypospadias, nor gives an estimation of severity to help plan surgical correction.

FIGURE 3-1 Classification of hypospadias.



Recently, classifications have been described that include the level of division of the corpus spongiosum, penile curvature, ventral hypoplasia, and relationship to the pubic bone. Many other anatomical factors which can interfere with the success of surgery and the final appearance of the genitalia can be taken into account in classifications, such as penile length, size of the glans, and quality of the urethral groove.²⁻⁶

A simple classification according to severity and based on a cost-benefit-ratio for the patient is:

- Mild hypospadias—distal isolated hypospadias (glandular, coronal, or penile) without associated chordee, micropenis, or scrotal anomaly. Indication for correction is mostly based on cosmetic issues. Surgical correction is only justfied when a low complication rate can be guaranteed.
- Severe hypospadias—scrotal and perineal or any type with chordee, micropenis, scrotal anomaly. Indication for correction is mostly based on functional issues. There is a higher complication rate. However, the benefit for the patient following surgery is substantial.
- Redo hypospadias. Indication for correction is to minimize burden following surgery.

3.3.1 **Recommendation and level of evidence**

Meatal location is only one of many prognostic and meaningful parameters including quality of tissues, curvature, size of glans, spongiosal division and others. The classification of hypospadias is an evolving picture and at the moment there is not one objective classification that is universally accepted (LOE: 3–5, GOR C–D).

3.4 How Should Preoperative Findings Be Documented?

Documentation of objective preoperative findings (as much as possible) helps establish prospective databases and is essential for audit and quality control. However, documentation is time consuming. Items which should be documented include^{7,8}:

- Age, height, and weight of the patient
- History of previous genital surgery
- Comorbidity
- History of androgen stimulation—form, dose, duration
- Associated testicular anomalies (unilateral or bilateral undescended testes)
- Site, shape, and width of the urethral orifice
- Shape, width, and size of the glans

- Presence and length of hypoplastic urethra proximal to the visible meatus
- Penile length
- Presence and degree of chordee of the penis on erection and without erection
- Site of division and quality of corpus spongiosum
- Morphology and quality of the foreskin
- Photo documentation may be taken into account

3.4.1 **Recommendation and level of evidence**

Documentation of objective findings will help to establish prospective databases and make future studies comparable. There is no consensus on objective penile assessment and documentation of preoperative findings (LOE 3–5, GOR B–D).

3.5 Further Tests and Evaluation— When, How, and by Whom?

Further tests and evaluations are offered practically for three reasons; the presence of associated upper urinary tract anomalies, the possibility of disorder of sexual development (DSD), and an associated prostatic utricle.

Hypospadias may be associated with other anomalies of the urinary tract, but the exact prevalence and significance of these anomalies is still controversial. From a recent systematic review, the frequency of anomalies varied from 0% to 56%, with most common anomalies being malposition of kidneys, vesicoureteral reflux, and hydronephrosis. The clinical advantage of ultrasonographic assessment of the upper urinary tract is unclear and controversial. It seems unwarranted in patients with isolated hypospadias.⁹⁻¹²

In case of suspicion of DSD (unilateral or bilateral undescended testes, micropenis), further investigations are warranted according to current guidelines.¹³

The prevalence of enlarged prostatic utricle in hypospadias is increased, but only a minority will become symptomatic. No evidence is available at the moment on screening (how to and the need to) for prostatic utricle in patients with hypospadias. Further evaluation should be performed in cases of recurrent infection or if any difficulty in passing the urethral catheter is encountered at the time of surgery.^{12,14}

3.5.1 **Recommendation and level of evidence**

At the moment routine evaluation of the upper urinary tract in an asymptomatic child presenting with hypospadias is not recommended. In the case of suspicion of DSD, further investigations are warranted according to current guidelines. No evidence is available at the moment on the need to screen and how to screen for prostatic utricle patients with hypospadias (LOE 3–5, GOR B–D).

3.6 When Should Hypospadias Be Corrected?

Based on expert opinion, an action committee of the American Academy of Pediatrics recommended that surgery of the male genitalia should better be performed between 6 and 18 months of age, and similar recommendations were expressed by the European Association of Urology guidelines.^{15,16}

These recommendations are based on the risk of surgery and anesthesia, cognitive development, genital awareness, emotional development, and psychosexual development, suggesting that genital surgery should ideally be completed in the first year of life.¹⁷ A recent cross sectional study however has questioned the current practice of early hypospadias repair, challenging the lack of evidence to support recommendation for an ideal age of repair.¹⁸ According to the authors the psychological and surgical outcome were not affected significantly when patients were operated before or after 18 months. In cases when surgery is postponed for any reason, hypospadias repair should be completed before the teenage years, since there is evidence that boys with hypospadias suffer from negative genital appraisal and sexual inhibitions and that self-reported health-related quality of life can be diminished.¹⁹

The effect of early repair on the surgical outcome is a subject of controversy. Although studies suggest a decreased incidence of complications in younger patients,^{20,21} other authors suggest that age is not a risk factor for urethral complications in hypospadias repair.²²

3.6.1 **Recommendation and level of evidence**

It is recommended that hypospadias repair be performed in infancy or early childhood, ideally when there is a trained pediatric anesthetist available. Evidence concerning the ideal age of hypospadias repair is weak (LOE 3–5, GOR B–D).

3.7 **Preoperative Androgens**

Androgen stimulation is commonly used prior to hypospadias repair when the penis and glans are small, and in redo surgery, with the aim of increasing penile size and also enhancing the quality of tissues.

There is neither consensus on the best type of androgen nor the correct way of application. Systemic beta-chorionic gonadotropin, systemic testosterone, local testosterone cream, and dehydrotestosterone (DHT) cream are some of the agents used in practice.²³⁻²⁵

Androgens increase penile size and have different effects on local tissues. Possible negative effects of androgen stimulation have not systematically been analyzed. They are generally thought to be transient and minor (mood, increased erections and pubic hair). There are no good data on long-term effects. Local androgen therapy is thought not to be associated with major side effects. However, since androgens have shown to have detrimental effects on wound healing and inflammation, the application of these substances have been criticized and it is recommended to stop therapy at least 3 months prior to surgery.²⁶

Two recent systematic reviews and meta analysis critically assessed the effect of preoperative androgen stimulation on surgical outcomes after hypospadias repair^{27,28} (LOE 2A and only 1 RCT). Published literature is of low quality and lacks standardized reporting with important patient and surgical details missing. The analysis could identify only one single randomized trial using topical DHT, which decreased the complication rate significantly.²⁹ There is no sufficient data on the effect of local estrogen in hypospadias repair.

3.7.1 **Recommendation and level of evidence**

Preoperative androgens should be reserved for severe hypospadias and a small penis. Application should be stopped prior to surgery to allow androgenic effects to vanish There is neither consensus on the best type of androgen nor on the correct way of application and the potential side effects of androgens have not been studied thoroughly. (LOE 2A–5, GOR B–D).

3.8 Preferred Technique for Hyposopadias Repair

An algorithm for approach to management of mild and severe hypospadias is shown in Figure 3-2.



Hypospadias

3.8.1 Mild hypospadias repair

Over the last years, the tubularized incised plate urethroplasty (TIP) repair (**Figure 3-3**), a variation of the Thiersch-Duplay urethroplasty, has become the most popular technique for distal hypospadias repair worldwide.³⁰⁻³² Large retrospective cohort studies and meta analysis have shown that the TIP technique is versatile, easy to apply, and gives good functional and cosmetic results with a low complication rate.³³⁻³⁸ The TIP procedure has been modified by using a skin or mucosal inlay in cases of small glans, urethral plate of dubious quality or redo cases (one randomized trial, LOE 2B).³⁹⁻⁴⁵ There is good data that the fistula rate can be decreased by covering the urethroplasty with a waterproofing layer of dartos tissue.⁴⁶⁻⁴⁸

The Mathieu urethroplasty and its modifications are also popular procedures with a low complication rate.⁴⁹ A recent review and single center studies comparing the TIP repair and Mathieu repair show that no technique appears to be definitely superior.^{50–56} In a systematic review there were no significant differences of complication rates between the two techniques, and the TIP technique was usually of better cosmesis.⁵⁷

FIGURE 3-3 TIP procedure (longitudinal incision of the urethral plate before tubularization)



Nevertheless, surgeons use many other techniques for the repair of distal hypospadias (meatal advancement and glanduloplasty, glans approximation procedure technique, urethral mobilization and advancement, personal modifications, etc.).^{30,58-60} The literature dealing with these techniques are mainly single surgeon, single center experiences and therefore subject to inherent bias and non-randomization.

3.8.2 **Recommendation and level of evidence**

The TIP repair is the most commonly used technique for the repair of distal hypospadias worldwide. There is good evidence in the literature to recommend this procedure (LOE: 2A, 2B, GOR B). However, high-quality randomized trials (follow-up rate >80% and long-term follow-up) are still missing. Therefore, personal experience, skill and surgical background will still play a major role in the choice of procedure (GOR D).

3.9 Severe Hypospadias

Repair of severe hypospadias is more complex than that of the mild hypospadias. Many factors interplay in the decision making and choice of the proper technique. Penile curvature, size of the penis, site of proximal division of the corpus cavernosum, quality of the urethral plate, scrotal transposition, quality of the foreskin and glanular size are factors affecting the choice of technique (**Figure 3-4**). In single center studies, it has been shown that of the many techniques for proximal hypospadias repair with or without preservation of the urethral plate (including two-stage repair, Thiersch-Duplay repair, TIP, Koyanagi, and tubularized and non-tubularized flap double based flap, and onlay urethroplasty) provide satisfactory functional and cosmetic outcome, with no significant differences and similar complication rates.^{61–80}

FIGURE 3-4 Severe hypospadias.



A recent systematic 20-year review could not show any superior surgical technique in the correction of severe hypospadias.⁸¹ However, the review was complicated by the low quality of primary literature. In three recent international specialist surveys looking at a variety of currently used techniques,³⁰⁻³² the most popular one worldwide seems to be the two-stage repair. This technique represents a reliable and easy to apply solution in severe hypospadias with small glans, chordee and tissues of doubtful quality.⁸² For most surgeons the presence of chordee is the crucial factor in deciding which technique to choose for the individual patient. After degloving of the penis and dissection of the ventral dartos tissues, assessment of the curvature is done by artificial erection. Several techniques have been described to correct chordee. Most of these techniques are based on the principles of shortening the dorsal side of the penis or lengthening the ventral part. Plication techniques have been suggested with or without mobilization of the neurovascular bundle. The dorsal midline incision minimizes the risk of injury to the neurovascular bundle.83 However, shortening of the penis is the most striking disadvantage of any plication technique. In contrast, grafting of the ventral side, the more aggressive approach, results in penile straightening without shortening. Many types of grafts have been suggested including dermal grafts, tunica vaginalis graft and flaps, buccal mucosa and small intestinal submucosa grafts.84-87

Extensive urethral plate mobilization has also been suggested for penile straightening without dissection of the urethra.⁸⁸⁻⁹⁰ Ventral corporotomy using multiple transverse incisions in the tunica albuginea of the corpus cavernosum, with no grafting, coupled with limited dorsal plications, if necessary to ensure sustained straightening, has also been successfully applied.⁹¹ In summary, a huge variety of techniques are applied for various degrees of chordee. There is no consensus or randomized trials that can substantiate the superiority of certain techniques. Moreover, there are no long term data on the influence of straightening techniques in erectile dysfunction in adulthood.

3.9.1 **Recommendation and level of evidence**

The two-stage repair by far is the most popular technique used in the correction of severe hypospadias. However there is no consensus on the ideal technique and there is no evidence in the literature that there is a definitely superior technique in the correction of severe hypospadias. Comparison between series is complicated by the lack of reliability in reporting outcomes, limited follow-up and failing to report long-term outcomes (LOE 3A–5, GOR C).

3.10 Foreskin Reconstruction or Circumcision?

The discussion of circumcision versus restoration of the foreskin is based on the cultural background of the patient. In routine clinical practice, a majority of the surgeons worldwide would perform circumcision. However, foreskin reconstruction can be offered to patients with mild hypospadias and adequate foreskin to perform the procedure. There is enough data (low-quality RCT LOE 2A) prooving that foreskin reconstruction can be performed safely.⁹²⁻⁹⁴ However, parents have to be informed that there might be an increased risk of complications related to foreskin reconstruction.⁹⁵

3.10.1 **Recommendation and level of evidence**

Foreskin reconstruction can be offered in mild hypospadias repair (LOE 2A, GOR B).

3.11 Urinary Drainage and Wound Dressing

Each surgeon has his or her own preference (**Figures 3-5** and **3-6**). Urine can be drained using a transurethral catheter, transurethral dripping stent or a suprapubic tube of various sizes. There is one prospective randomized trial showing the advantage of suprapubic diversion and using a stent in the anterior urethra. It is also recognized that in case of distal hypospadias, some surgeons prefer no drainage at all.^{6,12,16,96-102}

FIGURES 3-5 and 3-6 Examples of penile dressing and bladder drainage following hypospadias correction.



As is the case with urethral stenting, there is no hard data to suggest that one wound dressing could be better than another.^{6,16} Each surgeon has his preferred wound dressing for different reasons, and there is limited literature evidence from two prospective randomized trials showing no difference between postoperative dressing versus no postoperative dressing.^{12,103,104} There is consensus that wound dressing is important to obtain a proper immobilization of the penis, keeping the wound dry to allow better healing, reducing postoperative discomfort and stopping any bleeding preventing collection, especially under graft bed.

3.11.1 **Recommendation and level of evidence**

No clear evidence can highlight advantages of one or another form of drainage, although it seems logical to drain any reconstruction (LOE 2B–5, GOR B–D). However, there seems a consensus on the goals to be achieved by the wound dressing (LOE: 2B–5, GOR B–D).

3.12 **Perioperative Antibiotics**

For most surgeons the administration of prophylactic intravenous antibiotics at induction of anesthesia for hypospadias repair is the gold standard. Moreover, prophylactic oral antibiotics are given for a limited period of time postoperatively; usually as long as a urethral stent or catheter is in place. A variety of different antibiotics are in use.^{105,106} However, evidence for the use of prophylactic antibiotics is scarce. Some studies advocate the use of prophylactic antibiotics^{107,108} (LOE 1B), whereas others question the role of prophylactic antibiotics. No study addresses adverse effects of antibiotics or the problem of bacterial resistance.¹⁰⁹

3.12.1 **Recommendation and level of evidence**

Until further evidence is available, prophylactic broad spectrum antibiotics will be the standard in hypospadias surgery. However it is important to point out that prophylactic antibiotic versus no antibiotic in hypospadias repair should be subject for future controlled studies (LOE 1B, GOR B).

3.13 Follow–up and Outcomes

Traditionally, successful repair of hypospadias was defined as straight penis in erection, and a meatus near the tip of the glans, permitting voiding in a standing position and allowing sexual intercourse. However, modern surgery claims that it is possible to create a functionally and cosmetically normal penis. The vast majority of publications present single-center and single-surgeon retrospective case series with a limited follow-up period and a limited number of patients undergoing follow-up.¹¹⁰

3.13.1 **Follow-up**

There is no consensus in the literature for how long patients should have follow-up. It has been criticized that follow-up periods (especially in Northern America) are short, perhaps too short to draw proper conclusions on outcomes and complications.¹¹¹ On the other hand, some believe that most of the complications appear within a short period post-operatively. Therefore follow-up for 6 or 12 months or so appears to be sufficient.^{6,112} However, there is evidence that the real number of complications is only to be assessed in long-term follow up after puberty.^{113,114,115–117} Although the impact of hypospadias continues through adulthood and new techniques are continuously evolving, only few reports have discussed the long term outcomes hypospadias repair. Due to the rapid growth at the puberty, there is potential risk for new problems, for example an asymptomatic micro-fistula may start leaking (**Figure 3-7**), or the neourethra might fail to grow adequately during the pubertal growth causing new curvature or the penile shape and length may cause concerns.^{118–121} Critically, it has to be added that follow up is very time consuming and surgeons often do not have the capacitiy for routine uroflow, calibration or photography, unless the patients are part of a prospective study. At a minimum, parents should be informed about the long-term risk of fistula, curvature, and stenosis and the need for a follow-up visit at or after puberty.

FIGURE 3-7 Late-presenting fistula.



3.13.2 Outcomes

There are a growing number of articles reporting reliable and valid data like inclusion and exclusion criteria, study design, primary and secondary outcome parameters, follow-up, a detailed description of the surgical procedure and so on.¹²² Nevertheless, randomized trials in hypospadiology are extremely challenging and most of the time impossible.¹²³ In large systematic reviews looking at different techniques, no single procedure appears to be definitively superior to the others. These reviews criticize that there are no standardized algorithms for assessment of outcome. Comparison of studies therefore is complicated, if not impossible. A recent systematic review showed that there is a substantial lack of long-term data. Quality of data is influenced by low follow-up rate, heterogeneous patients and data, and a lack of validated questionnaires and control groups.¹²⁴

Assessment of outcome includes:

Cosmesis

Quality of psychosexual life Functional outcome (micturition, sexuality)

3.13.2.1 Cosmesis

Cosmetic appearance usually is assessed by the surgeon (Figures 3-8 and 3-9). This is prone to bias, inaccuracy and can be subjective. There are several objective and validated scores to evaluate outcome of hypospadias surgery; Mureau score, hypospadias objective scoring evaluation, pediatric penile perception score, Hadidi score and hypospadias objective penile evaluation score.^{125-128,7,129-131} The scores includes general appearance of penis, size of penis, glans appearance, appearance of the meatus, penile skin, curvature, etc. rated by patient, parents and surgeon. These scores are easy to apply, can be kept in the patients notes and allow simple retrospective statistical evaluation. However, theses scores are very time consuming and none of these scores have proven to be effective in in clinical routine or on long term basis. Objective assessment of outcome using standardized and validated photography has also been suggested.7,125,132

3.13.2.2 Functional outcome

Functional outcomes are just beginning to be reported in the literature (**Figures 3-10** and **3-11**). A recent systematic review recommends uroflow study after toilet training. Children with obstructed flow parameters or borderline flows should be followed until adulthood. However, until long-term follow-up studies clarify the significance of abnormal flow parameters, the significance of these studies remain uncertain.¹³³ Most of the studies using uroflowmetry observed that in about 3.7% to 14.7% of patients the Qmax is lower than the 95th percentile of the normograms.^{134–136}

FIGURE 3-8 Good cosmetic outcome.



FIGURE 3-9 Poor cosmetic outcome.







3.13.2.3 **Psychosexual outcomes**

The psychosexual aspect is far more difficult to evaluate. There are some studies assessing long-term psychosexual adjustment and sexual function matched with control groups; they include strength of libido, strength and duration of erection, penile appearance, penile size, curvature, problems with ejaculation (spraying, dribbling, retrograde ejaculation, premature ejaculation), masturbation activity, sexually activity, problems with intercourse, number of sexual partners, intimate relationships, and satisfaction with sexual life in general. These data are very limited, controversial and confusing.^{134,137–139}

Svensson *et al.* are among the pioneers who investigated the late sexual effects of previous hypospadias surgery in adulthood. They interviewed 34 men operated on during childhood for hypospadias and 36 men operated on for appendicitis during childhood. Interviews focused on past and present social, sexual and psychological concerns. No significant difference was noted between the two groups regarding the age at first ejaculation, but hypospadias patients reported their first intercourse later in comparison to the control group. They also observed that hypospadias patients had less capacity for social and emotional relations than the controls. Interestingly, they did not find any significant correlation between severity of hypospadias and number of sexual partners, self-assessed sexual drive and number of intercourse.¹⁴⁰

3.13.3 **Recommendation and level of evidence**

Long-term assessment should be designed in prospective studies. In a group of patients follow-up and adequate counseling will be necessary to adult life.. Currently, there is no consensus on how and how long patients should be followed up after hypospadias repair. Long-term data is missing.

Parameter	Measurement	Items
History	Questionnaire Patient notes	Age at time of operationType of operation complications
Voiding	Questionnaire	 Satisfaction with voiding stream Spraying and straining Spraying and straining Spraying and straining
	Uroflow	VolumeQmaxResidual volume
	Ultrasound	 Residual volume Prostate
	Score	 International Prostate Symptom Score Expanded Prostate Index Composite
Cosmesis	Questionnaire Physical examination	 Concern about abnormal appearance Satisfaction with result Penis size Ashamed/fear of undressing Being ridiculed Curvature
	Score	 Junior Genital Perception Scale Hypospadias Objective Scoring Evaluation Pediatric Penile Perception Score
Sexuality	Questionnaire	 Satisfaction with sexual function Masturbation Intercourse Relationship
	Score	 International Index of Erectile Function Sexual Summary Score Expanded Prostate Index Composite
Psychology	Questionnaire	Quality of lifeDepression
	Involvement of clinical psychologist	 Beck Depression Inventory Goldberg General Health Questionnaire Pediatric Quality of Life Inventory Spielberger State-Trait Anxiety Questionnaire Minnesota Multiphasic Personality Inventory Child behavior checklist Youth Self Report Self-Perception Profile for Adolescents Case Western Reserve University Function Questionnaire Self-esteem and Relationship Questionnaire

TABLE 3-3 Recommended parameters of follow-up to be recorded in future studies.

3.14 Who Should Operate on Hypospadias and How Many Procedures?

Hypospadias will be operated on by specialists trained in the field of hypospadiology, irrespective of their background in pediatric urology, pediatric surgery, adult urology or plastic surgery. This varies from country to country. From the consensus, it seems clear that hypospadias surgery should be performed by people who know the tricks of the trade, as some cases can be really challenging.^{6,16,30} Actually, it is even considered that minor hypospadias may be a misnomer, because what presents as distal hypospadias might have a very narrow urethral plate and extensive chordee release might be insufficient to get it straight. It is even said that in order to do hypospadias repair, one should be able to cover the whole range of the problem, otherwise refer the patient elsewhere. It is clear that redo-hypospadias is always trickier, and the results worse than in a well-performed primary repair. There is no consensus on the number of hypospadias repairs one should do before being qualified as a so-called hypospadiologist, but performing around 50 hypospadias per year seems to be adequate^{6,30,141}



3.15 **References**

- 1. Phillips B, Ball C, Sackett D, et al. Oxford Centre for Evidence-based Medicine–Levels of Evidence (Updated by Jeremy Howick March 2009). 2009.
- Duckett JW. Hypospadias, in Gillenwater JT, Grayhack JT, Howard SS, et al. (Eds): Adult and Pediatric Urology. St Louis, Mosby Year Book: 1966:2550–2565.
- 3. Hadidi AT: Classification of Hypospadias, in Hadidi AT, and Azmy AF (Eds): Hypospadias Surgery. Heidelberg; Springer: 2004:79-83.
- 4. Mouriquand PD and Mure PY. Current concepts in hypospadiology. BJU International. 2004;93 Suppl 3: 26–34.
- 5. Orkiszewski M. A standardized classification of hypospadias. Journal of Pediatric Urology. 2012;8:410-414.
- 6. Snodgrass W, Macedo A, Hoebeke P, et al. Hypospadias dilemmas: a round table. Journal of Pediatric Urology. 201;7:145–157.
- 7. Baskin L: Hypospadias. A critical analysis of cosmetic outcomes using photography. BJU International. 2001;87:534–539.
- El-Hout Y, Braga LH, Pippi Salle JL, et al. Assessment of urethral plate appearance through digital photography: do pediatric urologists agree in their visual impressions of the urethral plate in children with hypospadias? Journal of Pediatric Urology. 2010;6:294–300.
- 9. Chariatte V, Ramseyer P and Cachat F. Uroradiological screening for upper and lower urinary tract anomalies in patients with hypospadias: a systematic literature review. Evid Based Med. 2013;18:11–20.
- Gupta L, Sharma S and Gupta DK. Is there a need to do routine sonological, urodynamic study and cystourethroscopic evaluation of patients with simple hypospadias? Pediatric Surgery International. 2010;26:971–976.
- Friedman T, Shalom A, Hoshen G, et al. Detection and incidence of anomalies associated with hypospadias. Pediatric Nephrology (Berlin, Germany). 2008;23:1809–1816.
- Castagnetti M and El-Ghoneimi A. The influence of perioperative factors on primary severe hypospadias repair. Nat Rev Urol. 2011;8:198–206.
- 13. Hughes IA, Houk C, Ahmed SF, et al. Consensus statement on management of intersex disorders. Arch Dis Child. 2006;91:554–563.
- Kojima Y, Hayashi Y, Maruyama T, et al. Comparison between ultrasonography and retrograde urethrography for detection of prostatic utricle associated with hypospadias. Urology 2001; 57:1151–1155.
- 15. Timing of elective surgery on the genitalia of male children with particular reference to the risks, benefits, and psychological effects of surgery and anesthesia. American Academy of Pediatrics. Pediatrics. 1996;97:590–594.
- 16. Tekgül S, Riedmiller H, Gerharz E, et al. Guidelines on Paediatric Urology of the EAU, in Urology ESfP (Ed). 2013.
- 17. Schultz JR, Klykylo WM and Wacksman J. Timing of elective hypospadias repair in children. Pediatrics. 1983;71:342–351.
- Weber DM, Schonbucher VB, Gobet R, et al. Is there an ideal age for hypospadias repair? A pilot study. Journal of Pediatric Urology. 2009;5:345–350.
- Dodson JL, Baird AD, Baker LA, et al. Outcomes of delayed hypospadias repair: implications for decision making. The Journal of Urology. 2007;178:278–281.
- Ziada A, Hamza A, Abdel-Rassoul M, et al. Outcomes of hypospadias repair in older children: a prospective study. The Journal of Urology. 2011;185:2483–2485.
- Perlmutter AE, Morabito R and Tarry WF. Impact of patient age on distal hypospadias repair: a surgical perspective. Urology. 2006;68:648–651.
- Bush NC, Holzer M, Zhang S, et al. Age does not impact risk for urethroplasty complications after tubularized incised plate repair of hypospadias in prepubertal boys. Journal of Pediatric Urology. 2013;9:252–256.
- Koff SA and Jayanthi VR. Preoperative treatment with human chorionic gonadotropin in infancy decreases the severity of proximal hypospadias and chordee. The Journal of Urology. 1999;162:1435–1439.
- Chalapathi G, Rao KL, Chowdhary SK, et al. Testosterone therapy in microphallic hypospadias: topical or parenteral? Journal of Pediatric Surgery. 2003;38:221–223.

- Nerli RB, Koura A, Prabha V, et al. Comparison of topical versus parenteral testosterone in children with microphallic hypospadias. Pediatric Surgery International. 2009;25:57–59.
- Gorduza DB, Gay CL, de Mattos ESE, et al. Does androgen stimulation prior to hypospadias surgery increase the rate of healing complications? A preliminary report. Journal of Pediatric Urology. 2011;7:158–161.
- 27. Wright I, Cole E, Farrokhyar F, et al. Effect of preoperative hormonal stimulation on postoperative complication rates after proximal hypospadias repair: a systematic review. The Journal of Urology. 2013;190:652–659.
- Netto JM, Ferrarez CE, Schindler Leal AA, et al. Hormone therapy in hypospadias surgery: a systematic review. Journal of Pediatric Urology. 2013;9:971–979.
- 29. Kaya C, Bektic J, Radmayr C, *et al.* The efficacy of dihydrotestosterone transdermal gel before primary hypospadias surgery: a prospective, controlled, randomized study. The Journal of Urology. 2008;179:684–688.
- Springer A, Krois W and Horcher E. Trends in hypospadias surgery: results of a worldwide survey. European Urology. 2011;60:1184–1189.
- Cook A, Khoury AE, Neville C, et al. A multicenter evaluation of technical preferences for primary hypospadias repair. The Journal of Urology. 2005;174:2354–2357, discussion 2357.
- Steven L, Cherian A, Yankovic F, et al. Current practice in paediatric hypospadias surgery; a specialist survey. Journal of Pediatric Urology. 2013;9:1126–1130.
- Snodgrass W, Ziada A, Yucel S, et al. Comparison of outcomes of tubularized incised plate hypospadias repair and circumcision: a questionnaire-based survey of parents and surgeon. Journal of Pediatric Urology. 2008;4:250–254.
- 34. Akbiyik F, Tiryaki T, Senel E, *et al.* Clinical experience in hypospadias: results of tubularized incised plate in 496 patients. Urology. 2009;73:1255–1257.
- Braga LH, Lorenzo AJ and Salle JL. Tubularized incised plate urethroplasty for distal hypospadias: A literature review. Indian J Urol. 2008;24:219–225.
- 36. Snodgrass W, Koyle M, Manzoni G, *et al.* Tubularized incised plate hypospadias repair: results of a multicenter experience. The Journal of Urology. 1996;156:839–841.
- Sarhan OM, El-Hefnawy AS, Hafez AT, et al. Factors affecting outcome of tubularized incised plate (TIP) urethroplasty: singlecenter experience with 500 cases. Journal of Pediatric Urology. 2009;5:378–382.
- Snodgrass WT, Bush N and Cost N. Tubularized incised plate hypospadias repair for distal hypospadias. Journal of Pediatric Urology. 2010;6:408–413.
- 39. Mouravas V, Filippopoulos A and Sfoungaris D. Urethral plate grafting improves the results of tubularized incised plate urethroplasty in primary hypospadias. Journal of Pediatric Urology. 2013.
- Silay MS, Sirin H, Tepeler A, et al. "Snodgraft" technique for the treatment of primary distal hypospadias: pushing the envelope. The Journal of Urology. 2012;188:938–942.
- 41. Kolon TF and Gonzales ET, Jr. The dorsal inlay graft for hypospadias repair. The Journal of Urology. 2000;163:1941–1943 .
- 42. Tavakkoli Tabassi K and Mohammadi Rana T. Tubularized incised plate urethroplasty using buccal mucosa graft for repair of penile hypospadias. Urology Journal. 2012;9:514–521.
- 43. Shimotakahara A, Nakazawa N, Wada A, et al. Tubularized incised plate urethroplasty with dorsal inlay graft prevents meatal/ neourethral stenosis: a single surgeon's experience. Journal of Pediatric Surgery. 2011;46:2370–2372.
- 44. Schwentner C, Seibold J, Colleselli D, et al. Single-stage dorsal inlay full-thickness genital skin grafts for hypospadias reoperations: extended follow up. Journal of Pediatric Urology. 2011;7:65–71.
- Ferro F, Vallasciani S, Borsellino A, et al. Snodgrass urethroplasty: grafting the incised plate--10 years later. The Journal of Urology. 2009;182:1730–1734.
- 46. Yigiter M, Yildiz A, Oral A, et al. A comparative study to evaluate the effect of double dartos flaps in primary hypospadias repair: no fistula anymore. International Urology and Nephrology. 2010;42:985–990.
- Djordjevic ML, Perovic SV and Vukadinovic VM. Dorsal dartos flap for preventing fistula in the Snodgrass hypospadias repair. BJU International. 2005;95:1303–1309.

- Cimador M, Pensabene M, Sergio M, et al. Coverage of urethroplasty in pediatric hypospadias: randomized comparison between different flaps. Int J Urol. 2013;20:1000–1005.
- 49. Hadidi AT. The slit-like adjusted Mathieu technique for distal hypospadias. Journal of Pediatric Surgery. 2012;47:617-623.
- Scarpa MG, Castagnetti M, Berrettini A, et al. Urinary function after Snodgrass repair of distal hypospadias: comparison with the Mathieu repair. Pediatric Surgery International. 2010;26:519–522.
- Elganainy EO, Abdelsalam YM, Gadelmoula MM, et al. Combined Mathieu and Snodgrass urethroplasty for hypospadias repair: a prospective randomized study. Int J Urol. 2010;17:661–665.
- Aminsharifi A, Taddayun A, Assadolahpoor A, *et al.* Combined use of Mathieu procedure with plate incision for hypospadias repair: a randomized clinical trial. Urology. 2008;72:305–308.
- Moradi M, Moradi A and Ghaderpanah F. Comparison of snodgrass and mathieu surgical techniques in anterior distal shaft hypospadias repair. Urology Journal. 2005;2:28–31.
- 54. Imamoglu MA and Bakirtas H. Comparison of two methods--Mathieu and Snodgrass--in hypospadias repair. Urologia Internationalis. 2003;71:251–254.
- 55. Oswald J, Korner I and Riccabona M. Comparison of the perimeatal-based flap (Mathieu) and the tubularized incised-plate urethroplasty (Snodgrass) in primary distal hypospadias. BJU International. 2000;85:725–727.
- Wilkinson DJ, Farrelly P and Kenny SE. Outcomes in distal hypospadias: a systematic review of the Mathieu and tubularized incised plate repairs. Journal of Pediatric Urology. 2012;8:307–312.
- 57. Wang F, Xu Y and Zhong H. Systematic review and meta-analysis of studies comparing the perimeatal-based flap and tubularized incised-plate techniques for primary hypospadias repair. Pediatric Surgery International. 2013;29:811–821.
- 58. Duckett JW and Snyder HM, 3rd. The MAGPI hypospadias repair in 1111 patients. Ann Surg. 1991;213:620-625; discussion 625-626.
- 59. Zaontz MR. The GAP (glans approximation procedure) for glanular/coronal hypospadias. The Journal of Urology. 1989;141:359–361.
- 60. Thiry S, Gorduza D, Mouriquand P. Urethral advancement in hypospadias with a distal division of the corpus spongiosum: Outcome in 158 cases. J Pediatr Urol. 2013 Nov 16. pii: S1477–5131(13)00308-2. doi: 10.1016/j.jpurol.2013.10.019. [Epub ahead of print]
- Rigamonti W and Castagnetti M. Onlay on albuginea: modified onlay preputial island flap urethroplasty for single-stage repair of primary severe hypospadias requiring urethral plate division. Urology. 2011;77:1498–1502.
- 62. Obaidullah and Aslam M. Ten-year review of hypospadias surgery from a single centre. British Journal of Plastic Surgery. 2005;58:780-789.
- Ferro F, Zaccara A, Spagnoli A, *et al.* Skin graft for 2-stage treatment of severe hypospadias: back to the future? The Journal of Urology. 2002;168:1730–1733; discussion 1733.
- Djordjevic ML, Majstorovic M, Stanojevic D, et al. Combined buccal mucosa graft and dorsal penile skin flap for repair of severe hypospadias. Urology. 2008;71:821–825.
- Aoki K, Fujimoto K, Yoshida K, et al. One-stage repair of severe hypospadias using modified tubularized transverse preputial island flap with V-incision suture. Journal of Pediatric Urology. 2008;4:438–441.
- Macedo Jr A, Liguori R, Ottoni SL, et al. Long-term results with a one-stage complex primary hypospadias repair strategy (the three-in-one technique). Journal of Pediatric Urology. 2011;7:299–304.
- Patel RP, Shukla AR and Snyder HM, 3rd. The island tube and island onlay hypospadias repairs offer excellent long-term outcomes: a 14-year followup. The Journal of Urology. 2004;172:1717–1719; discussion 1719.
- Amukele SA, Weiser AC, Stock JA, et al. Results of 265 consecutive proximal hypospadias repairs using the Thiersch-Duplay principle. The Journal of Urology. 2004;172:2382–2383.
- de Mattos e Silva E, Gorduza DB, Catti M, et al. Outcome of severe hypospadias repair using three different techniques. Journal of Pediatric Urology. 2009;5:205–211; discussion 212–204.
- Sugita Y, Tanikaze S, Yoshino K, et al. Severe hypospadias repair with meatal based paracoronal skin flap: the modified Koyanagi repair. The Journal of Urology. 2001;166:1051–1053.
- 71. Moursy EE. Outcome of proximal hypospadias repair using three different techniques. Journal of Pediatric Urology. 2010;6:45–53.

- 72. Braga LH, Pippi Salle JL, Lorenzo AJ, *et al.* Comparative analysis of tubularized incised plate versus onlay island flap urethroplasty for penoscrotal hypospadias. The Journal of Urology. 2007;178:1451–1456; discussion 1456–1457.
- 73. Snodgrass W and Bush N. Tubularized incised plate proximal hypospadias repair: Continued evolution and extended applications. Journal of Pediatric Urology. 2011;7:2–9.
- 74. Bracka A. A versatile two-stage hypospadias repair. British Journal of Plastic Surgery. 1995;48:345–352.
- 75. Chandrasekharam VV. Single-stage repair of hypospadias using longitudinal dorsal island flap: Single-surgeon experience with 102 cases. Indian J Urol. 2013;29:48–52.
- 76. Hadidi AT. Proximal hypospadias with small flat glans: the lateral-based onlay flap technique. Journal of Pediatric Surgery. 2012;47:2151–2157.
- 77. Hadidi AT. Lateral-based flap: a single stage urethral reconstruction for proximal hypospadias. Journal of Pediatric Surgery. 2009;44:797–801.
- Gonzalez R, Smith C and Denes ED. Double onlay preputial flap for proximal hypospadias repair. The Journal of Urology. 1996;156:832–834; discussion 834–835.
- 79. Xu N, Xue XY, Li XD, *et al.* Comparative outcomes of the tubularized incised plate and transverse island flap onlay techniques for the repair of proximal hypospadias. Int Urol Nephrol. 2013 Sep 24. [Epub ahead of print]
- 80. Springer A and Subramaniam R. Split dorsal dartos flap transposed ventrally as a bed for preputial skin graft in primary staged hypospadias repair. Urology. 2012;79:939–942.
- Castagnetti M and El-Ghoneimi A. Surgical management of primary severe hypospadias in children: systematic 20-year review. The Journal of Urology. 2010;184:1469–1474.
- 82. Bracka A. The role of two-stage repair in modern hypospadiology. Indian J Urol. 2008;24:210–218.
- 83. Baskin LS and Duckett JW. Dorsal tunica albuginea plication for hypospadias curvature. The Journal of Urology. 1994;151:1668–1671.
- 84. Braga LH, Pippi Salle JL, Dave S, *et al.* Outcome analysis of severe chordee correction using tunica vaginalis as a flap in boys with proximal hypospadias. The Journal of Urology. 2007;178:1693–1697; discussion 1697.
- Hayashi Y, Kojima Y, Mizuno K, et al. Demonstration of postoperative effectiveness in ventral lengthening using a tunica vaginalis flap for severe penile curvature with hypospadias. Urology. 2010;76:101–106.
- Mokhless IA, Youssif ME, Orabi SS, et al. Corporeal body grafting using buccal mucosa for posterior hypospadias with severe curvature. The Journal of Urology. 2009;182:1726–1729.
- Elmore JM, Kirsch AJ, Scherz HC, et al. Small intestinal submucosa for corporeal body grafting in severe hypospadias requiring division of the urethral plate. The Journal of Urology. 2007;178:1698–1701; discussion 1701.
- Baker LA, Mathews RI and Docimo SG. Radical bulbar dissection to correct severe chordee and proximal hypospadias. The Journal of Urology. 2000;164:1347–1349.
- Bhat A. Extended urethral mobilization in incised plate urethroplasty for severe hypospadias: a variation in technique to improve chordee correction. The Journal of Urology. 2007;178:1031–1035.
- Snodgrass W and Prieto J. Straightening ventral curvature while preserving the urethral plate in proximal hypospadias repair. The Journal of Urology. 2009;182:1720–1725.
- Snodgrass W and Prieto J. Straightening Ventral Curvature While Preserving the Urethral Plate in Proximal Hypospadias Repair. The Journal of Urology. 2009;182:1720–1725.
- ElGanainy EO, Hameed DA, Abdelsalam YM, et al. Prepuce preserving versus conventional Mathieu urethroplasty for distal hypospadias - a prospective randomized study. Journal of Pediatric Urology. 2012;8:264–267.
- 93. Erdenetsetseg G and Dewan PA. Reconstruction of the hypospadiac hooded prepuce. The Journal of Urology. 2003;169:1822–1824.
- Snodgrass W, Dajusta D, Villanueva C, et al. Foreskin reconstruction does not increase urethroplasty or skin complications after distal TIP hypospadias repair. J Pediatr Urol. 2013 Aug;9(4):401–406. doi: 10.1016/j.jpurol.2012.06.008. Epub 2012 Jul 31.
- Klijn AJ, Dik P and de Jong TP. Results of preputial reconstruction in 77 boys with distal hypospadias. The Journal of Urology. 2001;165:1255–1257.

- Radwan M, Soliman MG, Tawfik A, et al. Does the type of urinary diversion affect the result of distal hypospadias repair? A
 prospective randomized trial. Ther Adv Urol. 2012;4:161–165.
- Xu N, Xue XY, Wei Y, et al. Outcome analysis of tubularized incised plate repair in hypospadias: is a catheter necessary? Urologia Internationalis. 2013;90:354–357.
- Ritch CR, Murphy AM, Woldu SL, et al. Overnight urethral stenting after tubularized incised plate urethroplasty for distal hypospadias. Pediatric Surgery International. 2010;26:639–642.
- Hardwicke J, Jones E and Wilson-Jones N. Optimization of silicone urinary catheters for hypospadias repair. Journal of Pediatric Urology. 2010;6:385–388.
- Lorenz C, Schmedding A, Leutner A, et al. Prolonged stenting does not prevent obstruction after TIP repair when the glans was deeply incised. Eur J Pediatr Surg. 2004;14:322–327.
- Leclair MD, Camby C, Battisti S, et al. Unstented tubularized incised plate urethroplasty combined with foreskin reconstruction for distal hypospadias. European Urology. 2004;46:526–530.
- Karakus SC, Koku N, Parmaksiz ME, et al. The effect of urethral catheter size on meatal stenosis formation in children undergoing tubularized incised plate urethroplasty. Urology Journal. 2014;10:1095–1098.
- 103. Van Savage JG, Palanca LG and Slaughenhoupt BL. A prospective randomized trial of dressings versus no dressings for hypospadias repair. The Journal of Urology. 2000;164:981–983.
- McLorie G, Joyner B, Herz D, et al. A prospective randomized clinical trial to evaluate methods of postoperative care of hypospadias. The Journal of Urology. 2001;165:1669–1672.
- 105. Hsieh MH, Wildenfels P and Gonzales ET, Jr. Surgical antibiotic practices among pediatric urologists in the United States. Journal of Pediatric Urology. 2011;7:192–197.
- 106. Springer A. The use of antibiotics in hypospadias surgery. Results from an international survey. Unpublished data 2013.
- Lee YC, Huang CH, Chou YH, et al. Outcome of hypospadias reoperation based on preoperative antimicrobial prophylaxis. Kaohsiung J Med Sci. 2005;21:351–357.
- 108. Meir DB and Livne PM. Is prophylactic antimicrobial treatment necessary after hypospadias repair? The Journal of Urology. 2004;171:2621–2622.
- 109. Kanaroglou N, Wehbi E, Alotay A, et al. Is there a role for prophylactic antibiotics after stented hypospadias repair? The Journal of Urology. 2013;190:1535–1539.
- 110. Springer A. Assessment of Outcome in Hypospadias Surgery A Review. Frontiers in Pediatrics. 2014;2:2.
- González R and Ludwikowski B. Re: "Snodgraft" Technique for the Treatment of Primary Distal Hypospadias: Pushing the Envelope: M. S. Silay, H. Sirin, A. Tepeler, T. Karatag, A. Armagan, K. Horasanli and C. Miroglu J Urol. 2012;188:938–942. The Journal of Urology. 2013;189:1170–1171.
- 112. Snodgrass W, Villanueva C, Bush NC. Duration of follow-up to diagnose hypospadias urethroplasty complications. J Pediatr Urol. 2013 Dec 7. pii: S1477–5131(13)00334-3. doi: 10.1016/j.jpurol.2013.11.011. [Epub ahead of print]
- Spinoit AF, Poelaert F, Groen LA, et al. Hypospadias repair at a tertiary care center: long-term followup is mandatory to determine the real complication rate. The Journal of Urology. 2013;189:2276–2281.
- Kiss A, Sulya B, Szasz AM, et al. Long-term psychological and sexual outcomes of severe penile hypospadias repair. The Journal of Sexual Medicine. 2011;8:1529–1539.
- 115. Barbagli G, Perovic S, Djinovic R, et al. Retrospective descriptive analysis of 1,176 patients with failed hypospadias repair. The Journal of Urology. 2010;183:207–211.
- 116. Perovic S, Barbagli G, Djinovic R, *et al.* Surgical challenge in patients who underwent failed hypospadias repair: is it time to change? Urologia Internationalis. 2010;85:427–435.
- 117. Mundy AR. Failed hypospadias repair presenting in adults. European Urology. 2006;49:774–776.
- Mieusset R and Soulie M. Hypospadias: psychosocial, sexual, and reproductive consequences in adult life. Journal of Andrology. 2005;26:163–168.

- 119. Singh JC, Jayanthi VR and Gopalakrishnan G. Effect of hypospadias on sexual function and reproduction. Indian J Urol. 2008;24:249–252.
- 120. Ebert AK, Bals-Pratsch M, Seifert B, *et al.* Genital and reproductive function in males after functional reconstruction of the exstrophy-epispadias complex–long-term results. Urology. 2008;72:566–569; discussion 569–570.
- 121. MacLellan DL and Diamond DA. Recent advances in external genitalia. Pediatr Clin North Am. 2006; 53:449-464, vii.
- 122. Snodgrass W. Hypospadias reporting-how good is the literature? The Journal of Urology. 2010;184:1255-1256.
- 123. Springer A and Subramaniam R. Re: Serdar Tekgul, Hubertus Riedmiller, Piet Hoebeke, *et al.* EAU guidelines on vesicoureteral reflux in children. Eur Urol. 2012;62;534–542. European Urology. 2012;62:e101; author reply e100.
- 124. Rynja SP, de Jong TP, Bosch JL, *et al.* Functional, cosmetic and psychosexual results in adult men who underwent hypospadias correction in childhood. Journal of Pediatric Urology. 2011;7:504–515.
- 125. van der Toorn F, de Jong TP, de Gier RP, et al. Introducing the HOPE (Hypospadias Objective Penile Evaluation)-score: a validation study of an objective scoring system for evaluating cosmetic appearance in hypospadias patients. Journal of Pediatric Urology. 2013;9:1006–1016.
- 126. Hadidi AT. Assessement of Outcome, in Hadidi AT, and Azmy AF (Eds): Hypospadias Surgery. Heidelberg, Springer, 2004, pp 90–92.
- 127. Mureau MAM, Slijper FME, Slob AK, *et al.* Satisfaction with Penile Appearance after Hypospadias Surgery: The Patient and Surgeon View. The Journal of Urology. 1996;155:703–706.
- 128. Holland AJ, Smith GH, Ross FI, et al. HOSE: an objective scoring system for evaluating the results of hypospadias surgery. BJU International. 2001;88:255–258.
- 129. Ververidis M, Dickson AP and Gough DCS. An objective assessment of the results of hypospadias surgery. BJU International. 2005;96:135–139.
- 130. Weber DM, Schonbucher VB, Landolt MA, *et al.* The Pediatric Penile Perception Score: an instrument for patient self-assessment and surgeon evaluation after hypospadias repair. The Journal of Urology. 2008;180:1080–1084; discussion 1084.
- 131. Weber DM, Landolt MA, Gobet R, *et al.* The penile perception score: an instrument enabling evaluation by surgeons and patient self-assessment after hypospadias repair. The Journal of Urology. 2013;189–193.
- 132. Akhavan A , Merguerian PA, Grady RW, *et al.* Digital photographic measurement in hypospadias: Validation and comparison to intraoperative measurement. J Pediatr Urol. 2013 Nov 7. pii: S1477–5131(13)00301-X. doi: 10.1016/j.jpurol.2013.10.012. [Epub ahead of print]
- 133. Gonzalez R and Ludwikowski BM. Importance of urinary flow studies after hypospadias repair: a systematic review. Int J Urol. 2011;18:757–761.
- 134. Rynja SP, Wouters GA, Van Schaijk M, *et al.* Long-term followup of hypospadias: functional and cosmetic results. The Journal of Urology. 2009;182:1736–1743.
- 135. Kumar MV and Harris DL. A long term review of hypospadias repaired by split preputial flap technique (Harris). British Journal of Plastic Surgery. 1994;47:236–240.
- 136. van der Werff JF, Boeve E, Brusse CA, et al. Urodynamic evaluation of hypospadias repair. The Journal of Urology. 1997;157:1344–1346.
- 137. Jiao C, Wu R, Xu X, *et al.* Long-term outcome of penile appearance and sexual function after hypospadias repairs: situation and relation. International Urology and Nephrology. 2011;43:47–54.
- 138. Bubanj TB, Perovic SV, Milicevic RM, *et al.* Sexual behavior and sexual function of adults after hypospadias surgery: a comparative study. The Journal of Urology. 2004;171:1876–1879.
- 139. Chertin B, Natsheh A, Ben-Zion I, et al. Objective and subjective sexual outcomes in adult patients after hypospadias repair performed in childhood. The Journal of Urology. 2013;190:1556–1560.
- 140. Svensson J, Berg R and Berg G. Operated hypospadiacs: late follow-up. Social, sexual, and psychological adaptation. Journal of Pediatric Surgery. 1981;16:134–135.
- 141. Wilcox D and Snodgrass W. Long-term outcome following hypospadias repair. World Journal of Urology. 2006;24:240–243.
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Disorders of Sex Development (DSD)

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4.1 Introduction

Disorders of sex development are a highly varied group of conditions that share the common features of altered embryogenesis and/or hormonal milieu leading typically to structural organ change and discordance between the blood karyotype, the gonads, and the internal and/or external genitalia. A clear understanding of normal genitourinary embryogenesis is necessary to understand the complexity of DSD and the reader is referred to Chapter 1: Embryology of the External Genitalia. In general, there are a critical set of autosomal and sex chromosomal genes and hormonal milieu that dictate the formation and differentiation of the gonad into either an ovary, testis, undifferentiated gonad, streak gonad, dysgenetic gonad, or ovotestis at the critical time in embryonic development. Subsequently, the gonadal quality dictates the position of that gonad and its hormone production (specifically insulin-3, testosterone and Müllerian inhibiting substance production from the testis). The sexually dimorphic development of the internal and external genitalia is dependent upon not only the hormonal production of the ginad but also the structural integrity and hormonal responsiveness of the genital tissue. It is upon this basic framework of understanding that DSD can be approached clinically.

We present a review of the current status of the definition and classification, diagnosis and initial evaluation, medical and surgical management, as well as outcomes, tumor risk, and future needs in the care of patients with disorders of sexual development and differentiation. We propose the following guidelines:

- The term "disorder of sex development" (DSD) should be used to describe any congenital condition with atypical development of the chromosomes, gonads, or anatomic sex
- Indications for a DSD evaluation include:
 - Hypospadias with associated cryptorchidism
 - Age-adjusted phallic size more than +2SD for a normal clitoris but less than -2SD for a normal penis
 - Normal-appearing phallus with or without hypospadias and bilateral non-palpable testes
 - Virilized female (enlarged clitoris, posterior labial fusion, single perineal opening)
 - Apparent female with an inguinal/labial mass
 - Family history of DSD (e.g. CAIS)
 - A discordance between genital appearance and karyotype
 - Syndrome with overt genital ambiguity (e.g. cloacal exstrophy)

- Initial physical examination should document gonadal presence, position, and quality, stretched phallic/clitoral length, glans and corporal diameter, labioscrotal fold fusion, symmetry, hyperpigmentation, and rugation, the number and quality of orifices on the perineum, and the position and patency of the anus
- Initial diagnostic testing should include blood karyotype, 17-hydroxylase (OH) progesterone, urinalysis, and serum electrolytes, and abdominopelvic ultrasound
- Providers should perform blood karyotype and pelvic US in the initial evaluation of nonvirilized older children with suspected DSD
- Blood karyotype, serum LH, serum testosterone, serum dehydrotestosterone (DHT), pelvic US, and steroid profile are clinically indicated in the initial evaluation of virilized older children with suspected DSD

- The decision of gender assignment must be based on individual circumstances and requires a multidisciplinary team of health professionals including pediatric urologists, endocrinologists, gynecologists, geneticists, neonatologists, social workers, and psychiatrists
- For patients with CAH, glucocorticoid replacement is the mainstay of medical therapy
- For patients with hypogonadism/gonadal dysgenesis, supplemental sex steroids at puberty may be necessary for development of secondary sexual characteristics and bone health
- Detailed DNA mutation testing should be performed in Y+ DSD patients with GD to determine tumor risk.
- In any patient with concern for DSD, a newborn circumcision should not be performed
- DSD patients raised as female desiring feminizing surgery (vaginoplasty, clitoroplasty, and labioplasty) should have surgery by surgeons expert in DSD reconstruction between ages 6 to 12 months or as adults
- In the case of DSD for male sex of rearing, a consultation by surgical specialists experienced in DSD care should evaluate and plan single stage or staged masculinizing surgery

(hypospadias repair, orchiopexy with or without gonadal biopsy, and/or scrotoplasty), targeting age 6 months for first surgery

- In order to prevent germ cell tumor development, early gonadectomy is recommended in all patients in high risk groups (GD with Y chromosomal material (Y+) and intraabdominal gonads, PAIS with nonscrotal gonads, Y+ syndromic DSD). Since sex of rearing may also impact decision for gonadectomy, gonadal biopsy with possible gonadectomy after puberty in lower-risk groups (CAIS, GD (Y+) with scrotal gonads, and PAIS with scrotal gonads) may be considered. Testicular tissue should be removed in ovotesticular DSD raised female
- A variety of outcomes should be prospectively followed in DSD patients including molecular diagnosis, gonadal pathological diagnosis, urinary function, sexual function, endocrine function, fertility, psychological outcomes, and quality of life
- Multi-institutional prospective collaborative registries and trials with a standard assessment of outcomes should be undertaken for further advancement of the diagnosis and management of DSD

4.2 **Definition and Classification**

As the understanding of the etiologies of disorders of sexual development and differentiation has improved, the classification and nomenclature has also changed. The umbrella term "disorder of sex development" (DSD) should be used to describe any congenital condition with atypical development of the chromosomes, gonads, or anatomic sex.^{1,2} Although still hotly debated, a classification system based on gonadal histology has been eliminated and the focus shifted to a chromosome based classification system with 3 groups (46,XY; 46,XX; and sex chromosome DSD; **Table 4-1**). Within each group there are multiple underlying etiologies and it is suggested that the most descriptive term of the underlying etiology of the disorder be used (such as "complete androgen insensitivity" or "5-alpha reductase deficiency").^{1,2} In addition, the controversial terms "intersex", "pseudohermaphrodite", "hermaphrodite", and "sex reversal" should be eliminated.^{1,2} Advantages of the new classification system include the integration of the progress in the molecular genetic aspects of the sexual development into the terminology and an increased sensitivity to the concerns of the patient.¹

The goal of the new terminology and classification is to not only encompass the traditional cases of "ambiguous genitalia" but also cases in which the external genitalia are unambiguous but are discordant with the karyotype, gonads, and/or internal genitalia.³ In addition, the term DSD also encompasses structurally malformed external genitalia cases such as aphallia, vaginal agenesis, cloacal anomalies, and cloacal exstrophy. However, for the purposes of this chapter, the focus will remain on "ambiguous genitalia" and the reader is referred to the ICUD chapters regarding the diagnoses in the "other" categories noted in (**Table 4-1**).

TABLE 4-1 DSD Classification

46,XY DSD "Under virilization"	46,XX DSD "Virilization"	Sex Chromosome DSD
Testicular Mal-development 1) Complete or partial gonadal dysgenesis (SRY, SOX9, WT1, DHH) 2) Ovotesticular DSD 3) Testicular regression	Ovarian Mal-development 1) Gonadal dysgenesis 2) Ovotesticular DSD 3) Testicular DSD (SRY+, SOX9 duplication)	47,XXY 1) Klinefelters 2) Variations (46,XX,SRY+)
 Androgen Deficiency 1) Androgen synthesis disorder (5-alpha reductase def, StAR mutations) 2) Androgen receptor mutation (CAIS, PAIS) 3) LH receptor defects (Leydig cell aplasia/hypoplasia) 4) Disorders of anti-Müllerian hormone (AMH) and AMH receptor (persistent Müllerian duct syndrome) 	 Androgen Excess 1) Steroidsynthesis disorder (CAH) 2) Fetoplacental (aromatase deficiency, POR) 3) Maternal causes (androgenic medications, virilizing tumors) 	45,X0 1) Turners syndrome 2) Variations (46,XX,SRY–)
Other 1) Syndromic associations 2) Severe hypospadias 3) Cloacal exstrophy 4) Aphallia	Other 1) Vaginal agenesis (MURCS, MRKHS) 2) Cloacal anomalies and exstrophy 3) Syndromic associations	45,X/46,XY or 45,XX/46,XY 1) Mosaicism 2) Mixed gonadal dysgenesis 3) Ovotesticular DSD 4) Chimerism

MRKHS, Mayer-Rokitansky-Küster-Hauser syndrome; MURCS, Müllerian, renal, cervicothoracic somite abnormalities *Adapted from Lee *et al.*¹ and Hughes *et al.*²

Genital ambiguity with 46,XX karyotype suggests virilization due to androgen excess, ovarian maldevelopment, or other structural anomalies. The vast majority have normal ovaries and female internal genitalia but excess exposure to androgen virilizes the external genitalia. Sources of the excess androgen include fetal adrenal gland abnormalities such as congenital adrenal hyperplasia (CAH), placental aromatase deficiency, maternal tumors, and maternal drug exposures.⁴ Rarely, genital ambiguity with 46,XX karyotype is associated with gonadal dysgenesis (GD), ovotesticular DSD, or testicular DSD. Genital ambiguity with 46,XY karyotype suggests undervirilization due to testicular maldevelopment, androgen deficiency, androgen insensitivity or other structural anomalies. These patients either have gonads that failed to differentiate into testes, or differentiate testes, but the internal genitalia may not differentiate normally. The main diagnostic categories include testicular dysgenesis/malfunction (GD, ovotesticular DSD and testicular regression); androgen deficiency (androgen biosynthetic defects, Leydig cell hypoplasia, 5-alpha reductase deficiency); Müllerian duct persistence; and end-organ complete or partial unresponsiveness to androgen (AIS).⁴

Finally, sex chromosome DSD encompasses patients with Turner (45,X) and Klinefelter (47,XXY) syndromes as well as their variants and patients with mosaic karyotypes.⁵ The most common DSD mosaic karyotype is 45,X/46,XY with the most common associated diagnosis of mixed gonadal dysgenesis (MGD).⁵

4.3 **Patient Presentation and Diagnostic Evaluation**

A majority of patients will present with overt genital ambiguity at birth. In the neonate, a multitude of physical examination findings should prompt an evaluation for DSD, (**Table 4-2**). Controversy exists regarding the need for investigation for DSD in patients with isolated hypospadias and/or cryptorchidism.⁶ Previous karyotype studies in children have found a chromosomal anomaly in 1.8-2% of boys with isolated cryptorchidism, 0-7% with isolated hypospadias, and 12.5%-25% with a combination of hypospadias and cryptorchidism.⁷ The incidence of chromosomal anomalies further increased in patients with bilateral cryptorchidism (2.9%-8.3%) as well as with associated anomalies such as dysmorphic faces (9.4-15% in hypospadias and 6.7-12.2% in cryptorchidism).^{7,8} Thus, a work up for DSD is not indicated for isolated unilateral cryptorchidism or hypospadias but should be considered for bilateral cryptorchidism, cryptorchidism in combination with hypospadias, as well as either diagnosis with the presence of associated congenital anomalies.

TABLE 4-2 Indications for DSD Evaluation

1) Hypospadias with associated cryptorchidism
2) Age-adjusted phallic size more than +2SD for a normal clitoris but less than -2SD for a normal penis
3) Normal appearing phallus with or without hypospadias and bilateral non-palpable testes
4) Virilized female (enlarged clitoris, posterior labial fusion, single perineal opening)
5) Apparent female with an inguinal/labial mass
6) Family history of DSD (e.g. CAIS)
7) A discordance between genital appearance and karyotype
8) Syndrome with overt genital ambiguity (e.g. cloacal exstrophy)
*Adapted from Hughes <i>et al</i> ² , Romao <i>et al</i> ⁵ , and Ahmed <i>et al</i> ¹⁰

The goal of the initial evaluation is to gather sufficient information for gender assignment and to rule out life threatening conditions such as salt wasting CAH.⁴ This initial evaluation should include a thorough maternal, prenatal, and family history, physical exam, and basic laboratory and imaging tests. Because of the complexity of the diagnosis and long term management of these patients, the evaluation and counseling should be undertaken by an experienced multi-disciplinary team of health professionals including pediatric urologists, endocrinologists, pediatric surgeons, gynecologists, geneticists, neonatologists, social workers, pathologists, radiologists, and psychiatrists.²

The initial clinical evaluation should query for a history of infertility and/or use of assisted reproductive techniques, maternal ingestion of drugs (particularly steroids or progesterones) and/or environmental exposures, maternal virilization, gestational hypertension, placental insufficiency, and consanguinity of parents.⁶ In addition, a thorough family history should be obtained focusing on history of unexplained infant deaths, amenorrhea, hypospadias, infertility, and DSD in relatives.⁶ Finally, it is important to assess the family's social network, previous discussions with the parents regarding the potential diagnosis, as well as the parents' general understanding of the DSD and their immediate concerns.¹⁰

The physical exam should begin with an assessment of the general health of the baby to rule out potentially life threatening problems such as severe dehydration and electrolyte abnormalities from salt-wasting CAH.⁵ The infant should also be evaluated for the presence of any dysmorphic syndromic features and well as mid-line defects and/or jaundice which may point towards an abnormality in the hypothalamic-pituitary axis.¹⁰

An examination of the external genitalia should document gonadal presence, position, and quality, stretched phallic/clitoral length and glans and corporal diameter, labioscrotal fold fusion, symmetry, hyperpigmentation, and rugation, the number and quality of orifices on the perineum, and the position and patency of the anus.¹¹ Virilized female genitalia usually exhibit variable degrees of clitoromegaly with pigmentation and rugation of the labial skin as well as a urogenital sinus and should be scored via the Prader Classification, (**Figure 4-1**).¹¹ Male undervirilization is portrayed by hypospadias and may also be associated with a bifid scrotum, ventral penile curvature, and penoscrotal transposition.¹¹ The stretched phallic and clitoral length (from pubic symphysis to tip of glans) should be compared to normative values $(3.5 \pm 0.4 \text{ cm male})^{12}$ and $(4 \pm 1.24 \text{ mm female})^{.13}$ In a term infant, phallic length less than 2.0 to 2.5 cm is considered a microphallus.⁴ In those presenting with apparently normal female external genitalia, palpation should be performed to rule out the presence of testes within inguinal hernias.⁶ If gonads are able to be palpated, they are typically testes and occasionally ovotestes.⁴ At the time of initial evaluation, it is best to document in the medical record the physical exam of the external genitalia using gender neutral terms, to prevent inadvertent insinuation by the healthcare team of gender assignment to the family.

FIGURE 4-1

Prader classification system for ambiguous genitalia with increasing stages of virilization. The spectrum ranges from a female phenotype with mild clitoromegaly to a male phenotype with hypospadias.

Used with permission from Ahmed et al.⁶ Normal ^Q I II III IV V Normal d'

The initial laboratory test should include blood karyotype, serum 17-OH progesterone, urinalysis, and serum Na, K, CO₂.¹ With regards to the blood karyotype, it should be kept in mind that mosaicism may be tissue dependent and the gonad itself is often different.^{4,6} Karyotypic analysis of tissue derived from genital skin, urine sample or other sources may be obtained to exclude tissue specific mosaicism. The initial abdominopelvic ultrasound will assess for the presence/absence and the position of the ovaries, testes, and uterus as well as for the presence of any associated anomalies of the kidneys and adrenal glands.¹⁴ Genitogram or magnetic resonance imaging to assess malformations of the vagina and uterus can be considered if the ultrasound does not provide sufficient information, but is rarely needed.^{6,14}

After the first clinical evaluation, diagnostic testing should be tailored to the DSD category. Providers may measure serum anti-Müllerian hormone (AMH), inhibin B, and/or perform human chorionic gonadotropin (hCG) stimulation testing in patients with 46,XY DSD and sex chromosome DSD with bilateral nonpalpable testes. In the past, hCG stimulation test was performed to determine whether functional Leydig cells are present and able to produce testosterone.⁴ However, AMH and inhibin B are secreted by Sertoli cells and AMH in particular is thought to potentially be more sensitive for the presence of testicular tissue than serum testosterone.^{4,15} Cystovaginoscopy is highly valuable in the pre-operative anatomic assessment of the urogenital sinus, vaginal length, and confluence relative to the urethra. Finally, laparoscopy may be necessary for delineation of the internal reproductive tract anatomy and to facilitate gonadal and/or genital skin biopsies. Gonadal biopsies are useful for the diagnosis of mosasicism and ovotesticular DSD and genital skin biopsies are useful to establish cell lines for androgen receptor binding assays, and for analysis of 5-alpha reductase activity.⁴

In 46,XX patients, the most common cause of DSD is CAH, secondary to 21-hydroxylase deficiency which is detected in ~90% to 95% of cases.⁴ Once CAH is confirmed, electrolytes must be watched closely as 70% of patients with 21-hydroxylase deficiency with have concomitant salt wasting.⁴ Confirmatory testing to assist is establishing the diagnosis include renin, aldosterone, adrenocorticotropic hormone, dehydroepiandrosterone, and androstenedione levels.⁶ A summary of suggestive laboratory results can be found in (**Table 4-3**).

Ten to twenty percent of patients with DSD may present later in life without genital ambiguity but rather with absent or delayed puberty, primary amenorrhea, a palpable gonad (i.e. testis or ovotestis) in a female, virilization in a female, or breast development or gross hematuria in a male.^{2,5} Examples of diagnoses in patients who present with delayed puberty include gonadal dysgenesis (pure or mixed), ovotesticular DSD, luteinizing hormone (LH) receptor defects, and 17-hydroxylase deficiency.¹⁶ Females presenting with primary amenorrhea should be evaluated for complete androgen insensitivity syndrome (CAIS) and vaginal agenesis syndromes such as MRKH. Female patients with virilization should be evaluated for non-classical forms of CAH.¹⁶ Providers should perform blood karyotype and pelvic US in the initial evaluation of non-virilized older children with suspected DSD. Blood karyotype, serum LH, serum testosterone, serum DHT, pelvic US, and steroid profile are clinically indicated in the initial evaluation of virilized older children with suspected DSD.¹⁶

Dysgenetic gonads carrying a Y chromosome, as observed in 46,XY pure gonadal dysgenesis, have a propensity toward malignancies. Therefore, it is mandatory that karyotype be analyzed in the context of dysgerminoma diagnosed in "girls" with a non-ambiguous female phenotype: the finding of mutations of genes involved in the early gonadal development (SF1) in 46,XY PGD patients should lead to familial screening, as other cases may be diagnosed among female siblings, and bilateral gonadectomy be performed before gonadoblastoma or malignant germ cell tumor arises.¹⁷

Finally, at any age, genetic counseling is recommended as certain diagnoses have a known genetic component such as androgen insensitivity syndrome (X-linked recessive) and CAH (autosomal recessive).⁴ In addition, the characterization of a number of genes implicated in the pathogenesis of DSD provide DNA tests which may assist in the diagnosis.⁴ Though the vast majority of virilized 46,XX infants will have CAH, only 50% of 46,XY children with DSD will receive a definitive diagnosis.^{2,18} Many of these children are labeled as PAIS, however, it is suggested that a diagnosis of AIS only be reserved for patients with confirmed androgen receptor mutations. In conclusion, there is not one diagnostic algorithm which fits all cases, however, some general recommendations can be made, (**Figure 4-2**).

Test	Diagnostic Finding		
17-hydroxyprogesterone level	Elevated in 21-hydroxylase deficiency		
11-deoxycortisol and 11-dexycorticosterone levels	Both elevated in 11-p-hydroxylase deficiency		
Testosterone to dihydrotestosterone ratio	$>$ 20: 1 is suggestive of $5\alpha\text{-reductase}$ deficiency		
AMH and inhibin B levels in 46,XY DSD	Normal postnatal values are suggestive of normal Sertoli cell function and at least 1 testis. Low levels are indicative of Sertoli cell dysfunction, AMH gene mutations, and gonadal dysgenesis		
AMH level in 46,XX DSD	Elevated postnatal values are suggestive of ovotesticular DSD		
Human chorionic gonadotropin (HCG) stimulation	No increase in testosterone indicates poorly functioning testicular tissue (anorchia, LH receptor defect, or nonfunctioning Leydig cells)		
HCG stimulation	An increase in testosterone indicates that there is either 5α-reductase deficiency or end-organ unresponsiveness to testosterone		
*Adapted from Moshiri <i>et al.</i> ¹⁴ and Josso <i>et al.</i> ¹⁶			

TABLE 4-3 Relevant Laboratory Tests and Results in DSD



4.4 Gender Assignment

Unequivocally, the diagnosis and care of DSD patients is highly complex and requires the expertise of a multidisciplinary clinical care team, (**Figure 4-3**). Every case and situation is unique and the decision of gender assignment must be based on individual circumstances and therefore only broad recommendations can be made. It is important to remember that gender assignment should be done in a timely fashion but it is not an "emergency" and thus ample time should be provided for parent-infant bonding, family adaptation, open discussion, reinforcing information, and reassessment of understanding with the family.^{19,20}

The multidisciplinary team must work together with the family to consider the three important factors which need to be taken into account when assigning gender: expected gender identity, sexual function, and fertility potential. Other factors that may be considered include genital appearance, gonadal malignant potential and need for gonadectomy, surgical options, prenatal androgen exposure as well as the views of the family and cultural practices.^{6,20} The external masculinization score (EMS) has been used to aid this process.⁶⁰

In the consideration of gender assignment it is important to note that psychosexual development has 4 components: gender identity, gender role, sexual identity, and sexual orientation.²¹ Psychosexual development is influenced by multiple factors including exposure to androgens, sex chromosomes, compliance, brain structure, social circumstance, and family dynamics.¹ There is increasing evidence that prenatal influence of sex hormones on the developing brain contribute to gender identity and

thus it is recommended that genetic males with micropenis, penile agenesis, or traumatic loss of the penis, as well as 46,XY males with PAIS, 17-hydroxysteroid dehydrogenase (HSD), or 5-alpha reductase deficiency be reared as male.²⁰ This is supported by evidence that over half of 5-alpha-reductase deficiency patients assigned female at birth live in adulthood as males where there is a potential for fertility.^{5,22} The majority of patients with 46,XX CAH and 46,XY CAIS patients identify as female despite exposure to elevated androgen levels during fetal life.^{1,23-25} It is recommended these patients are gender assigned as female in part because of the potential for fertility.⁵ More difficult situations include PAIS, partial gonadal dysgenesis where unfortunately up to 25% have dissatisfaction with gender assignment regardless if raised male or female.²⁶ Some authors have suggested assigning the male gender to XY patients with at least one functional testicle and reasonable penile tissue on palpation.⁵

Unfortunately, unhappiness with ones assigned sex, or gender dysphoria, occurs more commonly in DSD patients than the general population but it is difficult to predict those that will be unhappy based on the karyotype, prenatal androgen exposure, and degree of virilization.^{21,22,27} It is important to note that sex-typical behavior, sexual orientation, and gender identity are separate entities so for example, homosexual orientation (relative to sex of rearing) is not an indication of incorrect gender assignment.¹ All children should receive developmentally appropriate information from an early age and participate in decision making as soon as possible.²⁰ Atypical gender role behavior and ambivalence in gender identity should be recognized and supported if necessary.²⁰

FIGURE 4-3

An ideal multidisciplinary clinical care team for DSD patients. Additional team members can include retired clinicians with past experience and expertise in DSD. If possible, it is also advocated to incorporate other stakeholders, such as adults with DSD and/ or families affected by DSD as well as patient support groups and social workers.

(Diagram provided courtesy of K. Wolffenbuttel.)



4.5 Medical Management

For patients with CAH, glucocorticoid replacement with the goals of replenishing the lack of cortisol and suppressing excessive androgen production by means of negative feedback on release remains the mainstay of medical therapy.⁵ Hydrocortisone is the preferred drug in children because of its short half-life and it should be administered as crushed tablets.²⁸ In contrast to children, adults with classic 21-hydroxylase deficiency CAH may develop hypertension and thus also require mineralcorticoid replacement to suppress plasma renin activity as well.²⁹ In addition, adult women with 21-OHD CAH may develop polycystic ovarian syndrome and menstrual irregularity secondary to androgen excess which can be treated with oral contraceptive pills.²⁹ Finally, acne and hirsutism in these patients can be treated with spironolactone.²⁹ Medical noncompliance with corticosteroid therapy can also cause increasing clitoromegaly, virilization, and short stature due to premature epiphyseal plate closure.

With the exception of patients with CAH, most individuals with DSD do not require medical therapy during childhood.¹⁶ Females with DSD, such as those with Turner's syndrome, CAIS status post gonadectomy, and gonadal dysgenesis, will require estrogen replacement for breast development and bone health.^{16,30} In patients with a uterus, progesterone therapy should be added after the 1st year of therapy or after the first episode of withdrawal bleeding.¹⁶ While the optimal formulation, dose, and method of administration are controversial, replacement therapy should be initiated so patients experience puberty at the time of their peers.³⁰ In female patients with decreased androgen secretion, low-dosage androgen supplementation may be initiated to stimulate sexual hair growth and libido.¹⁶ Finally, short stature is a common feature of Turner's syndrome, affecting 95% of patients.³⁰ Growth hormone supplementation is the standard of care for girls with Turner's as should be considered once decreased linear growth velocity is present as it has been shown to accelerate growth velocity and improve adult stature.³⁰

Male patients with hypogonadism, such as those with Klinefelter's syndrome, gonadal dysgenesis and PAIS, may require testosterone supplementation at puberty for bone health and the initiation of secondary sexual characteristics. Options for testosterone replacement include intramuscular injections, oral testosterone undecanoate, or transdermal preparations.³¹ Providers should not use hormonal therapy to induce testicular descent in patients with DSD as evidence concerning this therapy shows low response rates with lack of evidence for long term efficacy.

4.6 Genital Surgery

The previously held philosophy of surgically removing or "fixing" the genitalia of DSD patients incompatible with the assigned gender is now under scrutiny. Instead, the current general philosophical approach to surgery is to preserve the function of all internal and external genital organs if surgery is elected during infancy or childhood. This way, 'no bridge is burned' by organ removal, which allows for the opportunity for gender conversion in adulthood if desired. In addition, the timing of surgical intervention remains controversial. Some providers advocate surgical genital correction before 18 months of age to foster early development, gender identity, and gender congruent body image.²⁰ Others, however, support a "full consent policy" which suggests that genital operations in children should only be performed if the health of the child is at risk and elective surgeries are postponed until children can provide consent.³²

In DSD patients raised female, the joint decision for feminizing surgery is a delicate and controversial one. In these cases, consultation by surgical specialists experienced in DSD care should evaluate single stage or staged feminizing surgery if needed, usually between ages 6 to 12 months for first surgery. Feminizing surgery may involve three main steps: vaginoplasty, clitoroplasty, and labio-plasty. The extent of feminizing surgery is controversial and requires individualization as not all patients need all surgical components. In addition, surgical techniques vary secondary to the level of confluence of the urogenital sinus.³³ CAH is the most commonly encountered and surgically treated patient in these cases.

Neonatal clitoromegaly in CAH cases regresses significantly as corticosteroid replacement therapy diminishes serum testosterone levels, making clitoroplasty unnecessary in many. Nowever, if corticosteroid noncompliance is common through childhood and adulthood, significant increases in clitoromegaly can occur. Thus, a conservative but seasoned approach is required. Advances in surgical correction of the virilized female include preservation of the neurovascular bundle to maintain clitoral sensitivity and corporal sparing clitoroplasty which does not ablate any functional tissue from the clitoris.³⁴ Under no circumstances should the enlarged clitoris be completely resected as was historically done. There are a variety of surgical approaches.

If a urogenital sinus exists, with conjoined urethra and vagina exiting a single perineal orifice, vaginoplasty will be required to exteriorize the vaginal orifice for tampon usage and penetrative sexual activity. Advances in the surgical repair of the urogenital sinus include the anterior sagittal transrectal approach vaginoplasty.³⁵ Finally, autologous buccal mucosal vaginoplasty offers a novel technique for total neovagina creation , vaginal lengthening, or the secondary repair of vaginal stenosis as well as for the creation of the external genitalia when tissues are lacking.^{36,83} Patients with DSD who are reared as males will require masculinizing surgery. In any patient where there is a concern for DSD, a newborn circumcision should not be performed. Again, it is recommended that surgical specialists experienced in DSD care should evaluate and plan single stage or staged masculinizing surgery targeting age 4 to 6 months for first surgery. Surgery may include hypospadias and chordee repair and/or scrotoplasty. In the absence of spontaneous testicular descent by six months of age and 46,XY or sex chromosomal DSD, orchiopexy with or without gonadal biopsy should be performed. This timeline could be compressed and accelerated in the face of bilateral cryptorchidism due to evidence of testicular damage beyond 18 months. Benefits of early surgery include possible improved fertility and testicular catch up growth. In addition to the penile reconstruction in 46,XY DSD, some ancillary procedures are sometimes necessary including excision of Müllerian remnants or dysplastic gonads.³³ The reader is referred to ICUD chapters 3 and 8, respectively, for surgical techniques on hypospadias repair and orchiopexy.

4.7 **Tumor Risk in Patients With DSD**

Gonadal tumors in DSD patients are mostly malignant type II germ cell tumors (GCTs), the seminomatous and non-seminomatous cancers. Within the testes, the precursor is known as carcinoma *in situ* (CIS). In the ovary and dysgenetics gonad, the similar lesions are referred to as dysgerminomas and non-dysgerminomas, with gonadoblastoma (GB) as precursor in the absence of testis development (known as testicularization).39

4.7.1 **Diagnosis and prevalence of GCTs in DSD**

In DSD-patients the risk for GCTs is related to presence of part of the Y chromosome in the karyotype of the germ cells.^{40,41} It has been demonstrated that a specific region on the Y chromosome, called GBY (gonadoblastoma locus on Y), is of crucial importance, which may be related to presence of an oncogene.⁴² Additional research supports the testis-specific protein on Y (TSPY), as most likely candidate. In patients lacking the GBY region, including the TSPY-gene, the GCT risk equals that of the general population.⁴³

Although in the presence of specific Y chromosomal material the GCT risk is increased, the actual prevalence varies greatly between the different diagnostic subgroups. Precise data on cancer risk are however not available, for various reasons, including the absolute lack of prospective studies. Based on a comprehensive review of the literature published in 2006, Cools and coworkers demonstrated that the various Y-DSD subgroups can be classified according to their cancer risk profile as high, intermediate, low and unknown risk, see (**Table 4-4**).⁴⁴

Risk group	Disorder	Risk (%)	Action needed	Studies, n	Patients, n
High	High GD1(+Y)2 intra- abdominal		Gonadectomy ³	12	>350
	PAIS nonscrotal	15	Gonadectomy ³	3	80
	Frasier	60	Gonadectomy ³	1	15
	Denys-Drash (+Y)	40	Gonadectomy ³	1	5
Intermediate	Turner (+Y)	12	Gonadectomy ³	11	43
	17ß-HSD	28	Watchful waiting, possible biopsy	2	7
Low	CAIS	0.8	Biopsy ⁴ and possible irrad/ gonadectomy	3	120
	Ovotesticular DSD	3	Testicular tissue removal in case of rearing female	3	426
	Turner (–Y₅)	1	None	11	557
Unknown ⁶	5a-Reductase	0	Unresolved	1	3
	Leydig cell hypoplasia	0	Unresolved	1	2
	GD (+Y) ² scrotal	Unknown	Biopsy ⁴ and irrad?	0	0
	PAIS scrotal gonad	Unknown	Biopsy ⁴ and irrad?	0	0

TABLE 4-4 Summary of Risk of Germ Cell Malignancy

Adapted with permission from Cools M, Drop SL, Wolffenbuttel KP, *et al.*⁴⁴ Summary of the risk of germ cell malignancy in the various forms of DSD, subdivided into high, intermediate, Iow, and possibly no risk. Recommended actions are indicated, as well as the number of studies and patients included in the survey. In case of PAIS, 17ß-HSD, and ovotestis, the decision regarding gonadectomy is largely determined by sex of rearing.

¹GD (including not further specified, 46XY, 46X/46XY, mixed, partial, complete).

²GBY region positive, including the *TSPY* gene.

³At time of diagnosis.

⁴Postpubertal biopsy should assess OCT3/4 and SCF immunohistochemistry on >30 seminiferous tubules. Irrad, local irradiation with 18Gy.

⁵If karyotype detects a marker chromosome, polymerase chain reaction for Y-chromosomal GBY sequences should be performed. ⁶Insufficient information to formulate recommendations.

It is important to note that this classification was generated based on meta-analysis of retrospective studies that sometimes were very limited in numbers as well as possibly affected by inconsistencies that could not be identified by the authors.⁴⁴ Therefore, theoretically the risks indicated may be both an overestimation by preferential reporting on cancer cases (publication bias) as well as an underestimation resulting from adopting an early prophylactic gonadectomy policy in more recent series.⁴⁵ In addition, the series did not include the most optimal diagnostic methods for identification of the earliest lesions. In fact, correct risk assessment requires a molecular genetic DSD diagnosis and consistent criteria for histological diagnosis of early germ cell malignancy in DSD-patients, which was lacking in the past. This has been overcome more recently by application of several markers for detection of malignant germ cells, like placental alkaline phosphatase,^{46,47} c-KIT,⁴⁸ AP-2 gamma,^{49,50} NANOG,⁵¹ and OCT3/4,⁵² the latter being the most informative and consistent marker to date.⁵³

In this context two issues are relevant allowing proper interpretation. First, the markers used are not cancer cell specific, as they are all present during normal embryonic development, and are typically lost during late fetal or early neonatal life.^{46,47,50,51} Second, prolonged expression of these embryonic markers in germ cells is rather common in patients with DSD as well as in conditions like cryptorchidism, in general resulting in a suboptimal gonadal environment (i.e. hypovirilization), and is considered as a mere delay in germ cell maturation. Misdiagnosing maturation delay based on prolonged marker expression as early germ cell malignancy may result in over diagnosis and over treatment.⁵⁴ To overcome this dilemma additional histological criteria have been developed to discern between maturation delay and malignant transformation in gonads of 46,XY DSD see Table 4-5.44,55,56

TABLE 4-5	Pathological differentiation criteria to distinguish maturation delay and CIS
	in XY individuals with undervirilization syndromes

	Maturation delay	Transition	CIS	
Age of patient	<1 y	Prepubertal	>1 y	
Location of OCT3/4- positive cells within seminiferous tubules	Intraluminal	Intraluminal and on the basal lamina	On the basal lamina	
Location of OCT3/4- positive cells within the gonad	.ocation of OCT3/4- positive cells within the gonadDiffuse consistentlyPositive cells limited to a region of tubules; maturation delay or no positive cells in the remainder of the gonadPositive cells limited of tubules; maturation no positive cells in the remainder of the gonadPositive cells limited to a region of tubules; maturation of tubules; maturation of the gonadPositive cells limited to a region of tubules; maturation of tubules; maturation 		Positive cells limited to a region of tubules; maturation delay or no positive cells in the remainder of the gonad	
Adapted with permission from Cools M. Drop SL. Wolffenbuttel KP. et al. 44				

Further fine tuning of the distinction between pre-malignant and delayed matured germ cells was achieved by the discovery of an additional immunohistochemical marker, stem cell factor (SCF), also known as KITLG, in 2008 by Stoop et al. In contrast to the other markers SCF is a specific marker, as SCF expression is absent in both fetal, pediatric and adult normal testes, and exclusively positive in all CIS and GB specimen.⁵⁷ It is clear that accurate diagnostic work-up of gonadal material from DSD patients requires an experienced pathologist with specific expertise in this field.58

Treatment in relation to GCT risk in specific DSD-subgroups 4.7.2

Research in recent years has provided significant additional insights in the actual cancer risk in specific Y-DSD subgroups. Patients with 45,X/46,XY mosaicism are phenotypically extremely heterogeneous.⁵⁹ In 87 gonadal samples from a group of 48 patients with 45,X/46,XY DSD the cancer rate correlated with the phenotype, as quantified by the external masculinization score (EMS).⁶⁰ In the group with solely Turner features, without any signs of virilization, the cancer rate was low (2.2%). In the group with ambiguity at birth (EMS <7) the cancer risk was high (52%), and in mildly undervirilized boys (EMS 7-12) the risk was intermediate (13%).⁶¹ Based on these results, a proposal for gonadal management in 45,X/46,XY DSD was proposed, see (Table 4-6).

In this context it is important to note that 95% of individuals with 45,X/46,XY mosaic karyotype are normal males⁶² and not included in the series represented. Although in these mosaic-Y individuals with normal male phenotype the actual gonadal cancer risk is unknown, it can be deduced from their normal male phenotype and descended testes that the tumor risk will probably be low.^{59,61} Studies like these are of great clinical importance to facilitate development of individualized treatment protocols in patients from various Y-DSD subgroups.

TABLE 4-6 Individualized gonadal management in 45,X/46,XY mosaicism.

Mild undervirilization (EMS \geq 7)				
Orchiopexy				
Peripubertal and postpubertal regular self-examination (every 3 months) and ultrasound (annually)				
Two gonadal biopsies with detailed immunohistochemical tumor risk assessment — At orchiopexy or between ages 1 and 9 years (prepubertal) — Between ages 17 and 25 years (postpubertal)				
Gonadectomy (or irradiation?) if intratubular germ cell neoplasia or premalignant gonadal biopsy findings (undifferentiated gonadal tissue, SCF+ germ cells, or OCT3/4+ germ cells located on the basal lamina)				
Ambiguous genitalia (EMS ≥ 7)				
Same approach as for mild undervirilization				
Gonadectomy at low threshold if: — Physical examination or ultrasound suggests tumor — Inability to place gonad in scrotum at orchiopexy — Inadequate hormone production leading to hormone replacement therapy				
Female phenotype				
Prophylactic gonadectomy If patient declines gonadectomy, careful surveillance with repeated biopsy				
Cryopreservation not indicated				

Adapted with permission from Cools M, Pleskacova J, et al.61

4.8 **Outcomes**

Unfortunately, long term outcomes for DSD patients are inadequate secondary to the heterogeneity of the disorders as well as the treatments and the retrospective nature of a majority of the studies. A recent review of outcomes provides a platform on which to build future studies for improvement in DSD patient management and transition to adult life.⁶³ A variety of outcomes should be prospectively followed in DSD patients including urinary function, sexual function, endocrine function, molecular diagnosis, gonadal pathological diagnosis, fertility, psychological outcomes, and quality of life.

As surgery for DSD usually involves the urinary tract, an assessment of urinary function should be performed.⁶³ Reviews of long-term results of hypospadias repair reports that patients with hypospadias have lower urinary tract symptoms including spraying, post-void dribbling, and feelings of incomplete emptying twice as often as controls.⁶⁴ In addition, females with CAH have reported an increase in urge, nocturnal, unexplained incontinence, and hesitancy.⁶⁵ In patients who have not yet

had surgery, it is still important to assess lower urinary tract function as the anatomical changes in 46,XX DSD can lead to incomplete emptying of the bladder, with pooling of urine in the common urogenital sinus, which in turn can lead to subsequent UTIs.⁶³

Monitoring of steroid and hormonal replacement therapies is mandatory among those patients who have enzyme deficiencies and/or require sex hormone supplementation. In addition, bone mineral density should be followed in patients with CAH and CAIS since they are at risk for bone loss second-ary to over suppression of androgens and loss of gonads respectively.⁶³ In addition, growth may be affected in patients on glucocorticoid replacement and those with CAIS and gonadal dysgenesis.⁶⁶ Finally, over exposure to androgens may result in early closure of bone growth plates if done in excess.

Long-term sexual function is extremely important to assess in patients with DSD. Patients who have 46,XY DSD report increased sexual problems including orgasm and arousal problems, sexual anxiety problems, problems in sexual communication, less sexual activity, less masturbation, and dissatisfaction with sexual function and genital appearance.^{67,68} Individuals with 46,XX DSD have global sexual dysfunction, low intercourse frequency, nonsexuality, avoidance, anorgasmia, and penetration difficulty.^{69,70} Studies in CAH specifically have found that 46% of patients reported their vagina was too small or narrow and 50% revealed that the disorder had affected their sex life.⁷¹ When compared with controls, women with CAH also reported more frequent pain and bleeding during intercourse as well as less overall satisfaction with their vagina.⁷¹ In addition, a larger proportion were not in a steady relationship (39%), not married (55%), had never been pregnant (74%), and had no children (76%) when compared to controls of the same age.⁷¹ It is likely that these difficulties are secondary to a combination of hormonal and psychologic factors surrounding the diagnosis as well as the treatments themselves. Previous reports have found in patients with CAH that genital sensitivity is impaired in areas where feminizing genital surgery had been done and impairment to sensitivity are linearly related to difficulties in sexual function.⁶⁹

With regards to surgical outcomes, despite evolution in the surgical reconstruction of virilized genitalia in CAH females, and recent advances improving the cosmetic and functional outcomes, the most common complication of this procedure still remains vaginal stenosis with published rates ranging from 36-83%.⁷²⁻⁷⁴ Although many recommend early vaginoplasty, re-operation rates vary from 62%–100% at or after puberty which prompts some to recommend delaying vaginoplasty until that time.⁷⁴⁻⁷⁷ Unfortunately, despite the high rates of vaginal stenosis, there have been no studies to evaluate pre-operative anatomic factors that predict vaginal stenosis in CAH girls with virilized genitalia. The reader is referred to ICUD chapters for long-term outcomes of orchiopexy (Chapter 3) and hypospadias repair (Chapter 8).

4.9 New Advances, Future Needs, Research Opportunities

There are many new exciting advances in the diagnosis of DSD. Cell-free fetal DNA testing, a noninvasive prenatal screening of fetal DNA in maternal circulation, can provide early sex identification and genotyping without amniocentesis or chorionic villus sampling, and thus decreases unnecessary prenatal CAH dexamethasone therapy.⁷⁸ In addition, recent advances in the field of whole genome/exome sequencing and comparative genomic hybridization microarray analysis have greatly improved the molecular diagnosis of DSD.⁷⁹ A list of genes known to be associated with DSD is listed in (**Table 4-7**). In the past, screening for mutations in the known sex-determining genes typically only identifies point mutations, while genomic rearrangements, such as copy number variations (CNVs), are often missed by sequencing and are too small to be detected by karyotyping.⁸⁰ Recent publications have identified causal CNVs in previously unexplained cases of 46,XY DSD.⁸⁰⁻⁸² As making the correct molecular diagnosis can have significant implications for gonadal tumor risk, gender assignment, response to hormone treatment, and need for family genetic counseling, it is reasonable to consider these novel technologies in DSD cases with an unexplained cause.

Gene(s)	Associated Condition		
RSP01	46,XX DSD and palmoplantar hyperkeratosis		
SOX9	46,XX DSD and campomelic dysplasia		
SRY	46,XX testicular DSD and 46,XY ovarian DSD		
CBX2, NROB, WWOX, AKR1C4, AKR1C2	46,XY DSD		
NR5A1	46,XY DSD and 46,XX premature ovarian failure		
DMRT, DMRT, MAP3K1	46,XY gonadal dysgenesis		
WNT4	46,XX DSD		
DHH	46,XY partial or complete gonadal dysgenesis		
LHX1	Mayer-Rokitansky-Küster-Hauser syndrome		
SOX3	46,XX and 46,XY DSD		
WT1	Frasier syndrome, Denys-Drash syndrome, WAGR (Wilms's tumor, aniridia, genital anomalies, mental retardation)		
GATA4	46,XY DSD or gonadal dysgenesis		
*Adapted from Baxter and Vilain. ⁷⁹			

TABLE 4-7 Genes Associated with DSD

continued on page 98

TABLE 4-7 Genes Associated with DSD, Cont'd

Gene(s)	Associated Condition		
AMH, AMHR2	Persistent Müllerian duct syndrome		
CYP11A, CYP17A, CYP21A2, HSD17B3, HSD3B2	САН		
POR	Cytochrome P450 oxidoreductase deficiency		
STAR	Cholesterol desmolase-deficient congenital adrenal hyperplasia		
AR	Complete or partial androgen insensitivity syndrome		
LHCGR	Leydig cell hypoplasia		
MAMLD1	Hypospadias		
ARX	X-linked lissencephaly with DSD		
ARL6, BBS1, BBS2, BBS4, BBS5, BBS7, BBS9, BBS10, BBS12, MKKS, TRIM32, TTC8	Bardet-Biedl syndrome		
CHD7, PROKR2, FGFR1, KAL, FGF8, PROK2	Kallmann syndrome		
GNRH1, GNRHR, TAC3, TACR3, KISS1R	Isolated abnormality in GnRH secretion or response		
SDR5A2	Complete or partial 5-alpha-reductase 2 deficiency		
*Adapted from Baxter and Vilain. ⁷⁹			

Unfortunately, there is still a long way to go as the majority of the DSD literature is level 3 or 4 evidence stemming from case series that lack a control group or are from expert opinion alone. In addition, the majority of the DSD research and patient care outcomes are challenged and hampered by the rarity and heterogeneity of these disorders. In the future, multi-institutional collaborative trials and registries are encouraged to overcome these challenges. In addition, providers should strive for assessment of outcomes in a standard manner. The evaluation of long-term outcomes for patients with DSD should be recorded in a prospective fashion over a period from birth to adulthood and beyond.⁶³

4.10 References

- 1. Lee PA, Houk CP, Ahmed SF, Hughes IA. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics. 118: e488-500, 2006.
- Hughes IA, Houk C, Ahmed SF and Lee PA. Consensus statement on management of intersex disorders. J Pediatr Urol. 2: 148-62, 2006.
- 3. Pasterski V, Prentice P, Hughes IA. Impact of the consensus statement and the new DSD classification system. Best Pract Res Clin Endocrinol Metab. 24: 187-95, 2010.
- 4. Ogilvy-Stuart AL, Brain CE. Early assessment of ambiguous genitalia. Arch Dis Child. 89: 401-7, 2004.
- Romao RL, Salle JL, Wherrett DK. Update on the management of disorders of sex development. Pediatr Clin North Am. 59: 853-69, 2012.
- Ahmed SF, Rodie M. Investigation and initial management of ambiguous genitalia. Best Pract Res Clin Endocrinol Metab. 24: 197-218, 2010.
- Moreno-Garcia M, Miranda EB. Chromosomal anomalies in cryptorchidism and hypospadias. J Urol. 168: 2170-2; discussion 2172, 2002.
- 8. Yamaguchi T, Kitada S, Osada Y. Chromosomal anomalies in cryptorchidism and hypospadias. Urol Int. 47: 60-3, 1991.
- Rohatgi M, Menon PS, Verma IC, et al. The presence of intersexuality in patients with advanced hypospadias and undescended gonads. J Urol. 137: 263-7, 1987.
- Ahmed SF, Bashamboo A, Lucas-Herald A, et al. Understanding the genetic aetiology in patients with XY DSD. Br Med Bull. 106: 67-89, 2013.
- Creighton S, Chernausek SD, Romao R, Ransley P, Salle JP. Timing and nature of reconstructive surgery for disorders of sex development - introduction. J Pediatr Urol. 8: 602-10, 2012.
- 12. Feldman KW, Smith DW. Fetal phallic growth and penile standards for newborn male infants. J Pediatr. 86: 395-8, 1975.
- 13. Oberfield SE, Mondok A, Shahrivar F, Klein JF and Levine LS. Clitoral size in full-term infants. Am J Perinatol. 6: 453-4, 1989.
- 14. Moshiri M, Chapman T, Fechner PY, *et al.* Evaluation and management of disorders of sex development: multidisciplinary approach to a complex diagnosis. Radiographics. 32: 1599-618, 2012.
- Zimmermann S, Schottler P, Engel W, et al. Mouse Leydig insulin-like (Ley I-L) gene: structure and expression during testis and ovary development. Mol Reprod Dev. 47: 30-8, 1997.
- 16. Lee PA, Houk CP. Disorders of sexual differentiation in the adolescent. Ann N Y Acad Sci. 1135: 67-75, 2008.
- Capito C, Arnaud A, Hameury F, Fremond B, Lardy H, Leclair MD and Heloury Y: Dysgerminoma and gonadal dysgenesis: the need for a new diagnosis tree for suspected ovarian tumours. J Pediatr Urol. 7: 367-72, 2011.
- Morel Y, Rey R, Teinturier C, Nicolino M, Michel-Calemard L, Mowszowicz I, Jaubert F, Fellous M, Chaussain JL, Chatelain P et al.: Aetiological diagnosis of male sex ambiguity: a collaborative study. Eur J Pediatr. 161: 49-59, 2002.
- Houk CP, Hughes IA, Ahmed SF and Lee PA: Summary of consensus statement on intersex disorders and their management. International Intersex Consensus Conference. Pediatrics. 118: 753-7, 2006.
- Thyen U, Richter-Appelt H, Wiesemann C, Holterhus PM and Hiort O: Deciding on gender in children with intersex conditions: considerations and controversies. Treat Endocrinol. 4: 1-8, 2005.
- 21. Zucker KJ: Intersexuality and gender identity differentiation. J Pediatr Adolesc Gynecol. 15: 3-13, 2002.
- Cohen-Kettenis PT: Gender change in 46,XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. Arch Sex Behav. 34: 399-410, 2005.
- Dessens AB, Slijper FM and Drop SL: Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. Arch Sex Behav. 34: 389-97, 2005.
- 24. Mazur T: Gender dysphoria and gender change in androgen insensitivity or micropenis. Arch Sex Behav. 34: 411-21, 2005.

- 25. Roche PJ, Butkus A, Wintour EM and Tregear G: Structure and expression of Leydig insulin-like peptide mRNA in the sheep. Mol Cell Endocrinol. 121: 171-7, 1996.
- Migeon CJ, Wisniewski AB, Gearhart JP, Meyer-Bahlburg HF, Rock JA, Brown TR, Casella SJ, Maret A, Ngai KM, Money J *et al.*: Ambiguous genitalia with perineoscrotal hypospadias in 46,XY individuals: long-term medical, surgical, and psychosexual outcome. Pediatrics. 110: e31, 2002.
- 27. Meyer-Bahlburg HF: Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. Arch Sex Behav. 34: 423-38, 2005.
- Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, Meyer-Bahlburg HF, Miller WL, Montori VM, Oberfield SE *et al.*: Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 95: 4133-60, 2010.
- 29. Auchus RJ and Arlt W: Approach to the patient: the adult with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 98: 2645-55, 2013.
- 30. Gonzalez L and Witchel SF: The patient with Turner syndrome: puberty and medical management concerns. Fertil Steril. 98: 780-6, 2012.
- Wilson JD, Rivarola MA, Mendonca BB, Warne GL, Josso N, Drop SL and Grumbach MM: Advice on the management of ambiguous genitalia to a young endocrinologist from experienced clinicians. Semin Reprod Med. 30: 339-50, 2012.
- 32. Wilson BE and Reiner WG: Management of intersex: a shifting paradigm. J Clin Ethics. 9: 360-9, 1998.
- 33. Vidal I, Gorduza DB, Haraux E, Gay CL, Chatelain P, Nicolino M, Mure PY and Mouriquand P: Surgical options in disorders of sex development (dsd) with ambiguous genitalia. Best Pract Res Clin Endocrinol Metab. 24: 311-24, 2010.
- Pippi Salle JL, Braga LP, Macedo N, Rosito N and Bagli D: Corporeal sparing dismembered clitoroplasty: an alternative technique for feminizing genitoplasty. J Urol. 178: 1796-800; discussion 1801, 2007.
- Salle JL, Lorenzo AJ, Jesus LE, Leslie B, AlSaid A, Macedo FN, Jayanthi VR and de Castro R: Surgical treatment of high urogenital sinuses using the anterior sagittal transrectal approach: a useful strategy to optimize exposure and outcomes. J Urol. 187: 1024-31, 2012.
- Samuelson ML and Baker LA: Autologous buccal mucosa vulvovaginoplasty for high urogenital sinus. J Pediatr Urol. 2: 486-8, 2006.
- 37. Kaftanovskaya EM, Feng S, Huang Z, Tan Y, Barbara AM, Kaur S, Truong A, Gorlov IP and Agoulnik AI: Suppression of insulin-like3 receptor reveals the role of beta-catenin and Notch signaling in gubernaculum development. Mol Endocrinol. 25: 170-83, 2011.
- Miller SA, Dykes DD and Polesky HF: A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 16: 1215, 1988.
- 39. Oosterhuis J and Looijenga L: Testicular germ-cell tumours in a broader perspective. Nat Rev Cancer. 5: 210-22, 2005.
- 40. Scully RE: Gonadoblastoma. A review of 74 cases. Cancer. 25: 1340-56, 1970.
- 41. Verp MS and Simpson JL: Abnormal sexual differentiation and neoplasia. Cancer Genet Cytogenet. 25: 191-218, 1987.
- Page DC: Hypothesis: a Y-chromosomal gene causes gonadoblastoma in dysgenetic gonads. Development. 101 Suppl: 151-5, 1987.
- 43. Lau Y, Chou P, lezzoni J, Alonzo J and Komuves L: Expression of a candidate gene for the gonadoblastoma locus in gonadoblastoma and testicular seminoma. Cytogenet Cell Genet. 91: 160-4, 2000.
- Cools M, Drop SL, Wolffenbuttel KP, Oosterhuis JW and Looijenga LH: Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. Endocr Rev. 27: 468-84, 2006.
- Pleskacova J, Hersmus R, Oosterhuis JW, Setyawati BA, Faradz SM, Cools M, Wolffenbuttel KP, Lebl J, Drop SL and Looijenga LH: Tumor Risk in Disorders of Sex Development. Sex Dev. 4: 259-269, 2010.
- Honecker F, Stoop H, de Krijger RR, Chris Lau YF, Bokemeyer C and Looijenga LH: Pathobiological implications of the expression of markers of testicular carcinoma in situ by fetal germ cells. J Pathol. 203: 849-57, 2004.
- Stoop H, Honecker F, De Krijger R, Bokemeyer C and Looijenga L, .H.J.: Differentiation and development of human female germ cells during prenatal gonadogenesis: an immunohistochemical study. Hum Reprod. 20: 1466-1476, 2005.

- Rajpert-De Meyts E and Skakkebæk NE: Expression of the c-kit protein product in carcinoma-in-situ and invasive testicular germ cell tumours. Int J Androl. 17: 85-92, 1994.
- Hoei-Hansen CE, Nielsen JE, Almstrup K, Sonne SB, Graem N, Skakkebaek NE, Leffers H and Meyts ER: Transcription factor AP-2gamma is a developmentally regulated marker of testicular carcinoma in situ and germ cell tumors. Clin Cancer Res. 10: 8521-30, 2004.
- Pauls K, Jager R, Weber S, Wardelmann E, Koch A, Buttner R and Schorle H: Transcription factor AP-2gamma, a novel marker of gonocytes and seminomatous germ cell tumors. Int J Cancer. 115: 470-7, 2005.
- Hoei-Hansen CE, Almstrup K, Nielsen JE, Brask Sonne S, Graem N, Skakkebaek NE, Leffers H and Rajpert-De Meyts E: Stem cell pluripotency factor NANOG is expressed in human fetal gonocytes, testicular carcinoma in situ and germ cell tumours. Histopathology. 47: 48-56, 2005.
- Looijenga LHJ, Stoop H, De Leeuw PJC, De Gouveia Brazao CA, Gillis AJM, Van Roozendaal KEP, Van Zoelen EJJ, Weber RFA, Wolffenbuttel KP, Van Dekken H *et al.*: POU5F1 (0CT3/4) identifies cells with pluripotent potential in human germ cell tumors. Cancer Res. 63: 2244-2250, 2003.
- 53. de Jong J, Stoop H, Dohle GR, Bangma CH, Kliffen M, van Esser JW, van den Bent M, Kros JM, Oosterhuis JW and Looijenga LH: Diagnostic value of OCT3/4 for pre-invasive and invasive testicular germ cell tumours. J Pathol. 206: 242-9, 2005.
- Looijenga LH, Hersmus R, Oosterhuis JW, Cools M, Drop SL and Wolffenbuttel KP: Tumor risk in disorders of sex development (DSD). Best Pract Res Clin Endocrinol Metab. 21: 480-95, 2007.
- 55. Cools M, van Aerde K, Kersemaekers AM, Boter M, Drop SL, Wolffenbuttel KP, Steyerberg EW, Oosterhuis JW and Looijenga LH: Morphological and immunohistochemical differences between gonadal maturation delay and early germ cell neoplasia in patients with undervirilization syndromes. J Clin Endocrinol Metab. 90: 5295-303, 2005.
- Hannema SE, Scott IS, Rajpert-De Meyts E, Skakkebaek NE, Coleman N and Hughes IA: Testicular development in the complete androgen insensitivity syndrome. J Pathol. 208: 518-27, 2006.
- 57. Stoop H, Honecker F, van de Geijn G, Gillis A, Cools M, de Boer M, Bokemeyer C, Wolffenbuttel K, Drop S, de Krijger R et al.: Stem cell factor as a novel diagnostic marker for early malignant germ cells. J Pathol. 216: 43-54, 2008.
- Hiort O, Wunsch L, Cools M, Looijenga L and Cuckow P: Requirements for a multicentric multidisciplinary registry on patients with disorders of sex development. J Pediatr Urol. 8: 624-8, 2012.
- Cools M, Wolffenbuttel KP, Drop SL, Oosterhuis JW and Looijenga LH: Gonadal development and tumor formation at the crossroads of male and female sex determination. Sex Dev. 5: 167-80, 2011.
- Ahmed SF, Khwaja O and Hughes IA: The role of a clinical score in the assessment of ambiguous genitalia. BJU Int. 85: 120-4, 2000.
- Cools M, Pleskacova J, Stoop H, Hoebeke P, Van Laecke E, Drop SL, Lebl J, Oosterhuis JW, Looijenga LH, Wolffenbuttel KP et al.: Gonadal pathology and tumor risk in relation to clinical characteristics in patients with 45,X/46,XY mosaicism. J Clin Endocrinol Metab. 96: E1171-80, 2011.
- 62. Chang HJ, Clark RD and Bachman H: The phenotype of 45,X/46,XY mosaicism: an analysis of 92 prenatally diagnosed cases. Am J Hum Genet. 46: 156-67, 1990.
- Schober J, Nordenstrom A, Hoebeke P, Lee P, Houk C, Looijenga L, Manzoni G, Reiner W and Woodhouse C: Disorders of sex development: summaries of long-term outcome studies. J Pediatr Urol. 8: 616-23, 2012.
- Rynja SP, de Kort LM and de Jong TP: Urinary, sexual, and cosmetic results after puberty in hypospadias repair: current results and trends. Curr Opin Urol. 22: 453-6, 2012.
- Callens N, van der Zwan YG, Drop SL, Cools M, Beerendonk CM, Wolffenbuttel KP and Dessens AB: Do surgical interventions influence psychosexual and cosmetic outcomes in women with disorders of sex development? ISRN Endocrinol. 2012: 276742, 2012.
- Han TS, Goswami D, Trikudanathan S, Creighton SM and Conway GS: Comparison of bone mineral density and body proportions between women with complete androgen insensitivity syndrome and women with gonadal dysgenesis. Eur J Endocrinol. 159: 179-85, 2008.
- Schonbucher V, Schweizer K, Rustige L, Schutzmann K, Brunner F and Richter-Appelt H: Sexual quality of life of individuals with 46,XY disorders of sex development. J Sex Med. 2012;9:3154-3170.

- 68. Kohler B, Kleinemeier E, Lux A, *et al.* Satisfaction with genital surgery and sexual life of adults with XY disorders of sex development: results from the German clinical evaluation study. J Clin Endocrinol Metab. 2012;97: 577-588.
- Crouch NS, Liao LM, Woodhouse CR, et al. Sexual function and genital sensitivity following feminizing genitoplasty for congenital adrenal hyperplasia. J Urol. 2008;179:634-638.
- Crouch NS, Creighton SM. Long-term functional outcomes of female genital reconstruction in childhood. BJU Int. 2007;100: 403-407.
- Nordenskjold A, Holmdahl G, Frisen L, et al. Type of mutation and surgical procedure affect long-term quality of life for women with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2008;93:380-386.
- Creighton SM, Minto CL and Steele SJ: Objective cosmetic and anatomical outcomes at adolescence of feminising surgery for ambiguous genitalia done in childhood. Lancet. 2001;358:124-125.
- Krege S, Walz KH, Hauffa BP, et al. Long-term follow-up of female patients with congenital adrenal hyperplasia from 21-hydroxylase deficiency, with special emphasis on the results of vaginoplasty. BJU Int. 2000;86:253-258; discussion 258-259.
- 74. Stikkelbroeck NM, Beerendonk CC, Willemsen WN, et al. The long term outcome of feminizing genital surgery for congenital adrenal hyperplasia: anatomical, functional and cosmetic outcomes, psychosexual development, and satisfaction in adult female patients. J Pediatr Adolesc Gynecol. 2003;16:289-296.
- 75. Azziz R, Mulaikal RM, Migeon CJ, *et al.* Congenital adrenal hyperplasia: long-term results following vaginal reconstruction. Fertil Steril. 1986;46:1011-1014.
- 76. Sotiropoulos A, Morishima A, Homsy Y, *et al.* Long-term assessment of genital reconstruction in female pseudohermaphrodites. J Urol. 1976;115:599-601.
- Alizai NK, Thomas DF, Lilford RJ, et al. Feminizing genitoplasty for congenital adrenal hyperplasia: what happens at puberty? J Urol. 1999;161:1588-91.
- Nichols N, Binta H, Fields PA, et al. Immunohistochemical localization of relaxin-like factor/insulin-like peptide-3 in the bovine corpus luteum. Ann N Y Acad Sci. 2005;1041:506-509.
- 79. Baxter RM, Vilain E: Translational genetics for diagnosis of human disorders of sex development. Annu Rev Genomics Hum Genet. 2013;14:371-392.
- Harrison SM, Campbell IM, Keays M, et al: Screening and familial characterization of copy-number variations in NR5A1 in 46,XY disorders of sex development and premature ovarian failure. Am J Med Genet A. 2013;161:2487–2494.
- Ledig S, Hiort O, Scherer G, et al. Array-CGH analysis in patients with syndromic and non-syndromic XY gonadal dysgenesis: evaluation of array CGH as diagnostic tool and search for new candidate loci. Hum Reprod. 2010;25:2637-2646.
- 82. White S, Ohnesorg T, Notini A, *et al.* Copy number variation in patients with disorders of sex development due to 46,XY gonadal dysgenesis. PLoS One. 2011;6:e17793.
- 83. Grimsby GM, Baker LA. The use of autologous buccal mucosa grafts in vaginal reconstruction. Current Urology Reports. 2014;15(8):428-434.



Classic Exstrophy

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5.1 Introduction

The exstrophic anomalies often referred to as the exstrophy-epispadias complex,¹ are considered a spectrum of embryological abnormalities related by certain principle anatomic features including:

- Epispadias—considered the least severe anomaly in this spectrum, the urethra is a partial or complete open plate (on the dorsal surface of the phallus in males).
- Classic bladder exstrophy—the most common of these unusual anomalies, the bladder is an open plate on the low abdominal wall and always includes epispadias.
- Cloacal exstrophy—the bladder and the ileocecal junction of the bowel are an open plate on the low abdominal. The severity can

vary but the hallmark is the symmetry of the defect and the association with other defects (spinal, renal, lower extremities, and cardiac).

• Exstrophy variants—In which partial manifestations are seen of the above anomalies. This condition presents a broad spectrum of variations and commonly lacks symmetry in the sagittal plane. The condition is also called atypical cloacal exstrophy and probably represents a different etiology.

Classic bladder exstrophy occurs at a rate of one per 10,000 live births to one per 50,000 live births.^{2,3} This anomaly has long been recognized to occur more commonly in males than females with a ratio of 3-6:1 reported in the literature. The anomaly represents an anterior herniation of the developing bladder and urethra which may result from an early lower abdominal wall defect possibly caused by premature apoptosis of the infra-umbilical membrane. The defect and subsequent herniation of posterior developing structures prevent the normal development of the lower abdominal wall and anterior fusion of the pelvis. The result is a flattened pelvis with wide diastasis of the symphysis pubis. As a consequence the anatomy and function of the bladder, genitalia, and bony pelvis are all impacted by this congenital anomaly.

This chapter will be divided into the following sections:

- 1. Genital and Sexual Function, Fertility and Pregnancy
- Pregnancy
 Bladder Function

- 3. Orthopedic Outcomes
- 4. Exstrophy and Malignancy Risk
- 5. Urinary Tract Infections and Renal Function

5.2 Genital and Sexual function, Fertility and Pregnancy

5.2.1 Methods

To evaluate male and female genital and sexual function a systematic literature search was performed in Medline from 1969 to 2008 using the following key words: fertility and pregnancy were searched for "exstrophy"[All Fields] AND (("fertility"[MeSH Terms] OR "fertility"[All Fields]) AND ("Issues"[Journal] OR "Issues (St Louis Mo)"[Journal] OR "issues"[All Fields])) as well as exstrophy[All Fields] AND (genital[All Fields] AND ("physiology"[Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms] OR "function"[All Fields])) and exstrophy[All Fields] AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) and exstrophy[All Fields] AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) and exstrophy[All Fields] AND (("sexual behavior"[MeSH Terms] OR ("sexual"[All Fields] AND "behavior"[All Fields]) OR "sexual behavior"[All Fields] OR "sexual"[All Fields]) AND ("physiology"[Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "sexual"[All Fields]) AND ("physiology"[Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms] OR "function"[All Fields])) with the following limitations: 1) English or German publications, 2) human studies, 3) clinical trials, 4) meta-analyses, 5) review, 6) randomized clinical trial, 7) comparative study, and 8) ages birth to 65 years.

During the relevant period from 1969 – 2013, we identified 369 articles irrespective of patients' gender related to genital and sexual function, fertility, and pregnancy; 256 articles were excluded, because they did not meet inclusion criteria for this section of the review. From the remaining 113 articles, 34 non-systematic reviews, 25 case reports and 19 articles were excluded to language, leaving 36 original articles for analysis. 14 of these studies dealt exclusively with female patients and 13 studies with males, whereas nine included both gender.

For the analysis, we extracted the number of female or male patients from each article. If necessary, new calculations were made. In the 23 articles about female adults 20 were clinical-based studies using retrospectively collected data, three of them were multicenter studies, one with a control group and one was designed as a prospective study. In these 23 articles, 626 female patients were enrolled. As a caveat, five series originated from Germany possibly and likely involved the same cohort albeit with a longer follow-up or evaluated under different clinical aspects.^{4,5–9} Patient median age was reported at 25.5 years in 18 studies (range 0.2–63 years). Two studies provided the age range from 16 to 43 years¹⁰ and 19 to 55 years.¹¹ Three studies involved mainly patients younger than 18 years.^{3,8,9} Information about follow-up was available from 6 studies; one further study reported the range from only 0.33 to 7 years.¹² Median follow-up was 19.6 years, with a range from 0.2 to 35 years.

From the 22 articles about male exstrophy individuals 14 were clinical-based, one was clinical-based with a control group, five were population-based and two involved multicenter population-based with a control group. In total 454 individuals were evaluated with a median age of 24.8 years (range 0.2–53 years). Seven series did not provide patient age, one series provided only the age range from 14 to 19 years.¹³ Median follow-up was 17 years, with a range from 0.2 to 53 years. As above, two series likely had partial overlap with the same patient cohort.^{14,15} All studies used medical chart reviews to

retrieve clinical data. Postal or personal interviews with non-standardized mostly local questionnaires were additionally used in thirteen studies. Three studies used standardized tests, one the performance test Symptom Checklist–90, and an adapted personality score test; two used a 36-item short form (SF-36) and the SF-36 medical outcomes study (MOS) to review psychosocial integration and quality of life in these patients together with a local questionnaire evaluating functional and social aspects.^{16,17}

5.2.2 General Recommendations

- 1. Female exstrophy patients may require vaginal reconstruction after the initial exstrophy closure. They are at higher risk than the general population of uterine and vaginal prolapse regardless of a history of pregnancy (GOR: C)
- 2. Female exstrophy patients who achieve a pregnancy should be considered a high risk pregnancy given their underlying congenital anomaly (GOR: C)
- **3.** Male exstrophy patients have decreased fertility. Early evaluation and use of assisted reproductive techniques should be considered and offered (GOR: C)
- 4. Both male and female exstrophy patients should be offered psychological support throughout their development to address concerns regarding genital appearance and sexual function (GOR: C)

5.2.3 Female Exstrophy

The studies of female exstrophy patients have been placed into two sections:

Studies on genital, sexual and psychosexual function.
 Studies on potential fertility and pregnancy management.

Female genital anatomy and reconstruction techniques have been well described in fundamental articles and textbooks. The exstrophic vagina is short and broad and the external genitalia are altered. The uterus, fallopian tubes and ovaries are felt to be normal. Four studies provided information about associated genital anomalies, such as müllerian duplication in 6 female patients out of 52 (12%)¹⁸ and two patients out of seven (29%).¹⁹ In older studies the absolute numbers of anomalies such as narrowed vagina, absent vagina, hematocolpos, vaginal septum, genital prolapse, bicornate uterus, uterus didelphis with septum vaginae, rectovaginal fistula, absent uterus and ovaries or absent uterus were provided but not the incidence. The numbers of genital anomalies may be as high as 10 in 14 patients and 30 in 56 patients.^{20,21} However, in these series, it is unclear whether some patients have multiple simultaneous anomalies, and whether cloacal exstrophy patients or patients with associated anorectal malformation were included.

We identified few studies reporting gynecologic history. For instance, the incidence of dysmenorrhea, was only reported in one study in 5 of 12 females (41.7%).¹¹ Because the vaginal introitus usually appears narrow and is anteriorly displaced, vaginal dilation, episiotomy or an introitoplasty may be required to allow satisfactory intercourse. There are several concepts of vaginal reconstruction referring to this. Some authors wait until women reach pubertal age and perform vaginoplasty only if it is required.²² Others recommend a simple episiotomy at the time of primary reconstruction. The reviewed studies do not provide adequate information about previous history, local vaginal findings

or initial surgery, or provide follow-up. However, we can say that 231 vaginoplasties were performed in 14 studies and involved 517 patients; corresponding to a median of 68% of the reported female exstrophy patients (range 11%–94%).

We identified seven studies including information addressing satisfaction after genital reconstruction, and one additional study that asked explicitly about dissatisfaction.²³ Three of these seven articles included exactly the same results of 94% satisfaction rate and patient numbers (n=17).⁴⁻⁶ However, no objective assessment criteria were used. In the seven reviewed series 94.1% of patients expressed satisfaction with their genital appearance (range 41.7%–100%). Dissatisfaction with their appearance was expressed in three studies with rates of 12%,⁵ 20.8%,²⁴ and 36.4%²³ of the included patients; 81% (range 41%–100%) stated to be sexual active. They had a median age of 28 years (range 20.7–35 years). Dyspareunia was described in five studies in a median of 20.8% (range 15.7%–33%)^{4,5,11,16,24}; 91% (range 29%–100%) of the responding females in seven studies stated to have orgasm.

5.2.3.1 Quality of life

Few studies addressed psychosocial or psychosexual development in the adult population. Three series commented on employment status with 48%, 72.7%, or 100% actively employed.^{16,23,25} Only one study gave information about urinary continence status, stating that 22% of the included patients were incontinent.²⁶ Close relationships and dating were reported in three studies in a median 92.8% of the included 29 female patients (range 81.8%–100%).^{4,23,27} A median of 92.8% were married in 11 studies.

Feitz found nine of eleven women with a median age of 32 years (range 20–51 years) had lower scores compared to the baseline population according to the performance test Symptom Checklist–90.²³ Two populations were analyzed with SF-36 respectively the SF-36 MOS to review overall health and well-being.^{16,17} Patient scores were statistically significant lower than normative population scores in general health and physical functioning.¹⁶ However, in so called continent patients (dry for more than 2 hours), significantly higher scores were reached in social functioning, vitality, mental health and mental component summary. Patients with urethral voiding scored significantly better than patients on clean intermittent catheterization (CIC). Most interestingly, scores did not differ for gender, number of surgical procedures, scar cosmesis, school, sexual life, fertility or renal function.¹⁶ The second study used the SF-36 in 13 female patients. As their patients reached results comparable to or above average for population-based norms, the authors intentionally did not go into details due to the small size of their cohort.¹⁷

5.2.3.2 Pregnancy

Since the first reports in 1958 pregnancy risks in the exstrophy population are well known and include complications like urinary tract infection, malpresentation resulting from pelvic anomalies, uterine prolapse, ureteral obstruction, and prolonged labor. In a cohort of 626 women 205 pregnancies were reported. 159 life births were counted, 9 pregnancies were terminated, 35 had miscarriages and information was missing for 2. In 12 studies 109 female individuals stated they want to have a child and tried to get pregnant. These were a median of 35.5% (range 10%–92%) of the included females. Data about potential fertility treatment were available from three studies, indicating that about a third of

the patients have used this option (26%, 28.6%, 33%).^{16,18,19} Deans *et al.* noted 21% of their patients conceived within one year after unprotected sexual intercourse, whereas the majority of 79% had a delay to conception.¹⁸ These authors concluded fertility is impaired in the female exstrophy population.

Complications during pregnancy included urinary tract infection in a median 28.6% (range 14.3%–100%), reported in five studies. Upper urinary tract diversion was necessary in 24% and 60% of patients in two series.^{18,28} Urinary retention occurred in eight patients from two series, in 37% and 7.1% of the reported cases.^{18,25} Deans *et al.* described pregnancy induced hypertension in six patients (32%).18 Mode of delivery was reported in 12 studies. Half of the women underwent exclusively delivery by caesarean section. Ninety-one babies were delivered by caesarean section, 11 complicated by premature delivery. The gestational age was reported in two series with a median of 36 weeks (range 28–29 weeks).^{18,27} In one series four neonatal deaths were reported (7%).¹⁸

Complications during caesarean section were reported in nine cases (10%) including intra-operative injuries such as ureteral transection, urethrocutaneous fistula, vesicocutaneous fistula, bowel adhesions, uterine rupture, wound infection, hemorrhage and ileal stoma prolapse.^{16,18,23,27} In the series by Deans *et al.* in 56 pregnant patients 42 augmentations and 27 Mitrofanoff stomas had been performed; 3 of these patients experienced severe intra-operative complications during caesarean section. The authors conclude that pregnancies are a high risk for the mother and the baby and need close supervision of a multidisciplinary team.^{18,20,25,28}

The defective pelvic floor predisposes to uterine prolapse, which usually occurs after childbirth but may be seen in the nulliparous patient. Uterine prolapse was reported in 13 studies. In nine series uterine prolapse was described before pregnancy; 69 female individuals had prolapse before pregnancy, this was median 12.5% of the included females (range 9.8%–52%). During pregnancy prolapse developed in a further 38 patients, 50% of the included patients (range 20%-100%). It is believed by most in the pediatric urology community that uterine prolapse is less common when osteotomy and primary closure of the anterior defect are performed early in life. However from the data of the reviewed articles, we could not conclude whether prolapse is more often seen after osteotomy or in open pelvis, or after urinary diversion or reconstruction. Furthermore, there were no measures of the symphysis demonstrating the effectiveness in osteotomy or anterior closure of the ring in longterm. However, in six series osteotomy was done in 79 patients, median in 35.6% (range 21%–100%). However, in these osteotomy series prolapse was reported in mean 12.5, 17.8% and 29.9% respectively.^{12,24,29} The group of Anusionwu et al. provided conclusive data in 67 females, indicating that pelvic exstrophy closure may prevent pelvic prolapse in real terms. Uni- and multivariate analysis showed that only diastasis was associated with pelvic organ prolapse, meaning the smaller the diastasis was, the more unlikely was the risk of prolapse. Osteotomy itself however was not associated with a smaller prolapse risk.29

5.2.4 Male exstrophy genital and sexual function

This section about male exstrophy patients will be divided into two sections:

- 1. Studies on the genital, sexual and psycho- 2. Studies on fertility.
- sexual function

The genital anatomy in male exstrophy and their reconstruction techniques have been well described. In 83% of 454 included male patients information was available about primary or secondary bladder reconstructions, as 173 patients from 13 studies underwent bladder reconstruction and 204 patients out of 15 studies had urinary diversion. No detailed information about penile reconstructive surgery was provided. Data were collected from medical charts review in all studies; additional information was gathered in 9 studies with semi structured surveys.

5.2.4.1 **Fertility and sexual function**

To the best of our knowledge no standardized exstrophy specific questionnaire to collect clinical relevant data exists for the evaluation of genital function. Ten studies included physical check-up of the exstrophy individuals, including transrectal ultrasound, sonography in two studies, intravenous pyelogram and laboratory tests.^{15,30,31} Sixty-two semen analyses were reported in 10 studies. However, because two groups included the same patient cohort for their articles several times, we excluded semen analyses from redundant studies.^{4,32} Methodology of semen analysis, however, changed remarkably over the last 40 years. Today, the WHO 5th standard from June 2010 is used. For analysis we aggregated the findings in the standard groups of azoospermia, normospermia, and oligospermia. Additionally information about the ejaculated volume was provided in five studies. In one study seminal parameter such as zinc, fructose, glucosidase and microbiological results of the semen fluid were reported.³² The number of examined patients was small and the range of the detected values too high to define a framework for future standard values. Andrologic history was only focused on the presence of epididymo-orchitis. No other andrologic risk factors or information about previous surgery were provided in the cited studies.

During genital examination objective penile length was measured in 44 patients in two studies. Salem *et al.* provided a penile length of 7.65 cm (range 6–9 cm) in a cohort of 28 patients.³⁰ Nerli at al. measured in their patients undergoing so called penile lengthening procedures preoperatively 5.4 cm (range 3.7–6.4 cm).³³ These lower values might be the result of selection bias, because all included patients were seeking surgical improvement of penile length. Additionally the authors advised their patients who were interested in having a longer penis to use a vacuum erection device for passive stretching of the corpora. The results after this treatment, however, were not assessed. Satisfaction of genital cosmesis was reported in 7 studies, showing an impressively high satisfaction rate of 82% with a range of 11% to 94%. However, selection bias cannot be excluded in a situation where data are collected by interview with the primary surgeon.

A median of 62.5% of patients (range 18.2%–100%) stated they were sexually active in 16 studies. In three studies, approximately half of the responding patients (36%, 50%, 64%) stated they were satisfied with their sexual performance.^{23,27,33} Thirteen studies described that 100% of the evaluated patients had erections. Only one study documented erections explicitly only in 36%.³³ Most probably only 5 patients, 36% of included patients with a median age of 23 years (range 18–27 years),

answered the questions regarding this topic, a fact that explains the low reported erection rate in this cohort. Curvature was reported in median 43% of the evaluated males (range 13.3%–78.6%). Orgasm occurred in 81.5% of the patients (range 55%–100%) but was reported only in 4 studies.^{23,33–35}

Although Woodhouse stated that ejaculation by definition is not normal in men with exstrophy, some kind of antegrade ejaculation was reported in as high as median of 77% (26%–100%) in 15 studies.^{36,37} However, ejaculation was impaired by retrograde semen emission in a median 45.5% (range 3.2%–78%). No ejaculation at all was present in 10.8% (range 6.3%–32%) in seven series. Erectile dysfunction was documented in three series with 28 patients (93%), three patients (12%), and one patient (0.3%).^{30,34,35}

Sixty-two semen analyses showed azoospermia in 21 examinations (33.9%), normospermia in 16 (25.8%) and oligospermia in 25 cases (40.3%). In addition, due to the heterogeneity of the included patient cohorts it was not possible to analyze, whether semen analysis results were better after urinary diversion or functional reconstruction. Ejaculated volume was measured below normal with a median of 1.03 ml (range 0.2–2.09 mL). Only in one center information about retrieval of the semen probe was given, in the other studies it remained unclear whether patients were specifically advised to milk the urethra to collect all whole semen fluid.³²

In nine studies, 58 married patients, produced 30 children reported. Reproductive techniques like intracytoplasmic sperm injection were necessary to achieve a pregnancy for some patients.³⁰ Five studies stated explicitly that no children were produced, whereas eight studies gave no clear information at all about this important topic.

A median of 33.3% (range 20%–71%) experienced epididymitis in 6 studies. In three studies including mainly diverted patients the epididymitis rate was median 25.7% (range 20%-29%), and seems significantly lower than after functional bladder reconstruction with a median 40.8% (37.5%, 44%).^{15,38} However, it remained unclear in the studies including patients after urinary diversion and reconstruction whether one group was more prone to epididymitis.^{34,38} In addition, no data were provided on the clinical management of the epididymitis and about the consequences on longterm testicular growth and function. Hormone analysis was done in the two similar studies with the same interesting result of normal hormonal parameters in over 80% of the exstrophy patients. However, FSH was high in up to 19% individuals indicating potentially a primary testicular failure in exstrophy patients.^{15,32} However, fertility of an individual cannot be deduced from the parameters included in this review. It must be recognized that fertility is a very complicated process including social, psychosocial, psychosexual preconditions as well as anatomic or physical conditions and co-morbidity. Although procreative capacity may severely be impaired in most exstrophy individuals, individual examinations with hormonal status and semen parameters including semen microbiology are necessary to provide adequate counseling and an adequate treatment plan for these individuals. However, one group stated that anatomic reconstruction with positioning of the verumontanum in the posterior urethra is a mainstay for potential future fertility.¹⁵

5.2.4.2 **Psychosocial Aspects**

Several standardized tests were used to score well-being and psychosocial integration. The SF36 and SF37 MOS were applied to 37 patients.^{16,17,33} The International Index of Erectile Function 15-item questionnaire was used in two publications including 41 patients with a median age of 18 and 26 years (range 14–35 years).^{30,35} Castagnetti *et al.* used the International Index of Erectile Function-15 in 19 patients with a median age of 27 years (range 18.3–41.2 years) and compared the results to an age-matched control group.³⁹ Health condition, socioeconomic status and symptom checklists were in various combinations applied to 47 young patients with a median age approximately about 14.5 years (range 11–53 years).^{23,40,41} In these cohorts the Youth Self Report was routinely applied in two articles for 36 mainly younger pre- and peri-pubertal patients.

Six studies demonstrated a median of 40.8% of patients engaged in relationships and dating (range 21.4%–80%). Only two studies evaluated anxiety around sexual activity in exstrophy patients. Ebert et al. noted anxiety in 23.8% of their adult patients.¹⁵ Reiner et al. detected anxiety about sexual activity in 93% of their 19 patients in the age between 14-19 years. He raised the concern that these patients might develop psychosexual dysfunction later.⁴⁰ An important surrogate marker for this disturbance was the fact that only 14.2% of these individuals masturbated, a rate that should be much higher in general in that age group. Reiner et al. verified in addition psychiatric diagnoses in half of the reported adolescents in this age group. Diseth et al. found in the same age group 58% masturbating but confirmed psychiatric diagnosis in 50% of their patients. Additionally 72% claimed to have no friend to confide about these problems.⁴¹ Information about psychiatric diagnosis was provided in two studies in addition to these two already reported studies. Both included nearly the same cohort, finding psychiatric problems needing treatment in as high as 23.8%.¹⁵ From the 5 studies using the SF36 instrument to assess health and general well-being, only three gave clear information about the results.^{17,33} Overall, patients did not show significant restriction in physical activity and no overt mental health disturbances were present in these patients, although anxiety and depression were seen in younger individuals. Most probably age-related and puberty-related concerns might have a significant influence as the anomaly itself.

5.3 Continence and Exstrophy

5.3.1 Introduction

In the management of exstrophy, absence of urinary leakage and volitional voiding remains one of the goals of treatment. But it is a challenging goal in the management of this population. The achievement of urinary continence can come a the price of increased risk of urinary tract infection, renal deterioration, and increased risk of malignancy in addition to the morbidity of the operations that are often required to achieve urinary control. Urinary continence may be achieved by a variety of means including urinary diversion such as the ureterosigmoidostomy or its derivatives like the Mainz pouch or by anatomic approaches to exstrophy repair such as radical soft tissue mobilization (the Kelly repair), complete primary repair for exstrophy (the Mitchell repair), or the modern staged exstrophy repair (staged approach).
In this review, we will discuss the available data for the specific approaches and aggregate data available in the literature. One of the significant limitations in evaluating this outcome is the wide variability in the definition of continence used in these studies. The limited methods used by authors to assess urinary outcomes also significantly impact the utility of the data in these series. Most of the data was extracted by medical record review in a retrospective fashion.

5.3.2 Methods

To evaluate continence and exstrophy a systematic literature search was performed in Medline from 1969 to 2008 using the following key words: fertility and pregnancy were searched for exstrophy[All Fields] AND (("continence"[MeSH Terms] OR "continence"[All Fields]) AND ("Issues"[Journal] OR "Issues (St Louis Mo)"[Journal] OR "issues"[All Fields])) as well as exstrophy[All Fields] AND (bladder function [All Fields] AND ("physiology"[Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "function"[All Fields] OR "function"[All Fields]])) and exstrophy[All Fields] with the following limitations: 1) English or German publications, 2) human studies, 3) clinical trials, 4) meta-analyses, 5) review, 6) randomized clinical trial, 7) comparative study, 8) ages birth to 65 years old.

5.3.3 **Recommendations**

- 1. Primary anatomic reconstruction should be attempted when possible
- 2. Bladder capacity should be assessed to determine optimal options for continence if the patient remains incontinent
- 3. Urinary diversion can be considered in the setting of failed exstrophy repair or for patients in a resource-poor region

5.3.4 **Reported Continence Outcomes**

For this review, we identified 890 published manuscripts that met the initial review criteria. On further review, 92 met inclusion criteria and contained enough information to further evaluate the patients in these series for urinary control. We were able to evaluate continence outcomes for an aggregate of 2,711 patients. Only 60 studies (65%) used a specific definition for the term "urinary continence." The most frequent definition used in the literature as noted by Lloyd and his colleagues in an excellent review of reported continence in the exstrophy population was "dry with voiding/ catheterization every 3 hours" which was employed in 24 studies that defined continence. These authors also noted a trend toward improved reporting of methods for continence ascertainment in more recent years (p=0.02). Of the 2,681 children in their review, 1,372 (51%) were dry by the definition used by the authors of the respective studies.⁴² This data is similar to data reported by Gupta *et al* in an adult population of 65 patients with 20 years of follow-up who self reported a 50% urinary continence rate.⁴³

5.3.5 **Complete primary repair of exstrophy (CPRE)**

The longest series reporting outcomes of CPRE is from Seattle Children's Hospital, spanning 20 years. Median follow-up for 39 patients was reported as 58 months. When the authors assessed children older than 4 years of age, 74% reported daytime continence with volitional voiding and 20% of boys and 43% of girls achieving continence without bladder neck reconstruction or tailoring. Bladder neck procedures prior to achieving continence were performed for other children in the series. The majority of these bladder neck modifications were performed at the same time as ureteral reimplantation procedures and were performed using a Mitchell bladder neck technique. An 18% complication rate was reported in this series.⁴⁴ In another series using CPRE, Borer and colleagues noted that 5 of 8 patients (63%) 4 years old or older had grossly inadequate bladder outlet resistance and either had or will require bladder neck reconstruction.⁴⁵ This same group also reported on urodynamic findings between patients who had undergone exstrophy repair using a complete primary repair universally had bladder stability and bladder compliance versus those who had been repaired compared to a staged approach. Bladder capacity was equivalent between the two groups. Interestingly, patients repaired with a complete repair technique also had normal electromyelography results during this study.⁴⁶

5.3.6 **Radical soft tissue mobilization (RSTM)**

The RSTM technique (Kelly technique) has been employed for decades but has been enjoying increasing popularity over the last 5-10 years. This approach does not require osteotomies since the periosteum is mobilized from the pubic symphysis to Alcock's canal to allow the soft tissues of the bladder, bladder neck, and urethra to be approximated in the midline. Using this technique, Jarzebowski and colleagues reported long-term partial or complete continence rates at 70%. The majority of patients in this series did not require bladder augmentation or clean intermittent catheterization. However, on long-term assessment, the abdominal wall is considered to have an abnormal appearance in most adults closed with this technique.⁴⁷ Others have also successfully used this technique in the shortterm. Reported complications with the RSTM include bladder neck cutaneous fistulas and penile loss.⁴⁸

5.3.7 Modern staged exstrophy repair

Using the staged approach to exstrophy reconstruction continence rates have ranged widely as have definitions of urinary continence. Some authors have generally noted low rates of urinary continence— as low as 9%—with the need for clean intermittent catheterization to achieve urinary continence in as many as 60% of these patients.⁴⁹⁻⁵¹ Others have reported continence rates with volitional voiding of 70%.⁵² These series reflect the variable success of staged reconstruction. Long-term conversion rates in these patients from reconstructive efforts to urinary diversion range from 7.4% to 59.4%.^{51,53,54}

Aggregated data from several series employing staged reconstructions suggests that early exstrophy closure, if combined with pelvic ring approximation, results in a higher rate of continence achieved without the need for augmentation. Furthermore, if the exstrophy is repaired in a delayed fashion,

especially in cases without osteotomies, bladder capacity is more frequently inadequate for continence.^{55,56} Bladder capacity under anesthesia, prior to bladder neck plasty, appears to be an important benchmark of eventual urinary continence.⁵⁷

5.3.8 Urinary Diversion

Proponents of urinary diversion for the treatment of exstrophy argue that the varying continence rates achieved with functional reconstruction demonstrate the unreliability of this approach.⁵⁸ The use of the native bladder will often require later bladder augmentation with intestinal segments to achieve a functional bladder storage capacity. Certainly some centers report poor rates of continence after primary reconstruction and some urodynamic studies do demonstrate low urine flow rates and poor contractility in patients following primary bladder reconstruction.^{59, 60}

Primary urinary diversion avoids the complications associated with functional reconstruction including urinary retention and subsequent kidney damage, a predisposition to urinary tract infection, and later dependence on clean intermittent catheterization to empty the bladder with its own possible complications of urethral stricture formation, epididymitis, and urinary tract infection.⁶¹ Advocates of early urinary diversion also cite a decreased risk of epididymitis and obstruction of the vas deferens by the creation of a seminal receptacle with a suprapubic window at the level of the prostatic urethra.⁶¹

Urinary diversion may be used to provide urinary continence in patients who have failed multiple attempts at functional reconstruction.⁶² Some also advocate primary urinary diversion for patients with bladder plates deemed too small to close or in resource-poor regions.

Various investigators have made significant improvements on the use of the rectum as a urinary reservoir including the Mainz II Pouch and the Sigma Pouch.^{58,101} Use of a rectal reservoir permits urinary continence without reliance on clean intermittent catheterization. Hohenfellner and Stein report a 92% rate of renal preservation in their series of children treated primarily with a urinary rectal reservoir (Mainz II pouch since 1991). Continence rates of 97% in school-age children are reported in using this technique.⁶¹ The Heitz-Boyer-Hovelaque procedure involves isolation of a rectal segment for ureteral implantation followed by posterior sagittal pull-through of the sigmoid colon through the anal sphincter to achieve both urinary and fecal continence with separate anal openings for each. A small series using this procedure reported continence rates of 95% with acceptable complication rates.⁶³

Complications of rectal diversion include fecal-urinary incontinence in patients with impaired anorectal sphincter control.⁶⁴ Metabolic electrolyte imbalances can be treated with complete frequent emptying of the rectal reservoir reducing the contact time between urine and the absorptive mucosa, along with oral bicarbonate replacement. Oral bicarbonate replacement is recommended for all patients who have a base deficit of 2.5 mmol/L or greater.⁶¹ The risk of malignant degeneration still remains with use of a rectal urinary reservoir. If the increased risk of adenocarcinoma is due to conversion of urinary nitrates into carcinogenic nitrites by fecal bacteria, modifications of the rectal reservoir to prevent admixture of feces and urine may theoretically decrease the incidence.⁶¹ Long-term results are not yet available.

5.4 Orthopedic Factors in the Exstrophic Patient

The bony pelvis of the patient with classic bladder exstrophy is diastatic. The anterior portion is foreshortened and rotated laterally. As a consequence the pubic symphysis is separated with no union of the symphysis. This is associated with a fascial separation as well. Traditionally, the use of osteotomies has been considered an important point of consideration for exstrophy management with the use of anatomic exstrophy repair at an early age with the exception of the radical soft tissue or Kelly repair.

5.4.1 **Methods**

To evaluate the orthopedic issues involved with exstrophy a systematic literature search was performed in Medline from 1969 to 2008 using the following key words: exstrophy[All Fields] AND ("orthopaedic"[All Fields] OR "orthopedics"[MeSH Terms] OR "orthopedics"[All Fields] OR "orthopedic"[All Fields]) and with the following limitations: 1) English or German publications, 2) human studies, 3) clinical trials, 4) meta-analyses, 5) review, 6) randomized clinical trial, 7) comparative study, 8) ages birth to 45 years old. During the relevant period till 1969 PubMed showed 54 articles. After reading, 18 were judged as irrelevant. In addition 5 reviews and 6 case reports were excluded due to methodology of the review.

The review will be divided into three sections:

- 1. Studies on the congenital orthopedic issues associated with exstrophy.
- 2. Studies on technical aspects of primary and redo osteotomies.
- 5.4.2 **Congenital Orthopedic Issues**

Information about congenital orthopedic issues associated with exstrophy is found in three articles.⁶⁵⁻⁶⁷ In two clinical studies 51 patients were enrolled and the patients had a standardized radiographic assessment of pelvis, the hip and the spine. One study examined human stillborn fetuses and defined the distance from the posterior superior iliac spine to the ischial tuberosity to be about 40 mm, and the width between the two posterior superior iliac spines to be 25 mm.⁶⁶ Another study analyzed the anatomy of the lumbar spine of 28 exstrophy and five cloacal exstrophy patients at an average age of 8 years. They noted abnormal lumbosacral segmentation in five, congenital scoliosis and kyphosis in 4, partial sacral agenesis in three and interpedicular lumbar widening in two as signs for associated orthopedic developmental malformation.⁶⁷ Interestingly, it was found, that although exstrophy patients were affected in 36% with spinal abnormalities, these anomalies were predominantly present in cloacal exstrophy patients (80%).⁶⁷

3. Studies on the long-term outcomes of the osteotomies.

Sponseller *et al.* described in 1995 with his landmark publication the preoperative anatomy of the pelvis in exstrophy and defined the measures in comparison to age-matched controls and epispadias patients.⁶⁸ Symphysis diastasis in exstrophy was median measured with 42 mm, there was remarkably asymmetry in the pelvis, malformation of the sacro-iliac joints and occasional hip dislocation.⁶⁸ Sponseller *et al.* described an external rotation of the posterior and anterior pelvis, a retroversion of the acetabula, an 30% shortening of the pubic rami in comparison to normal controls and a progressive symphysis diastasis over time.⁶⁸ This study provided an exact description of the anatomy in the newborn exstrophy. The anterior defect as well as anterior outward rotation of the pelvic structures provides important information for the planning of the orthopedic surgical treatment and further understanding of postoperative recurrent symphysis diastasis.

5.4.3 Osteotomies

We identified 14 different osteotomy types reported in the literature. Pediatric orthopedic specialists explain this variety of osteotomies with mostly slight modifications of the incision line. Therefore after reading the methodology of surgery we combined the 14 different techniques into the following 5 groups:

- Transverse anterior innominate, Salterlike osteotomy includes transverse anterior innominate, the anterior innominate, anterior, horizontal and anterior supra-acetabular osteotomy
- 2. Transverse innominate/posterior combined, Sponsellers' osteotomy includes as well the innominate / vertical iliac and the combined vertical / transverse osteotomy
- **3**. Iliac osteotomy as oblique and diagonal anterior iliac osteotomy
- 4. Ramotomy including ischiopubic osteotomy because it has the same effect and
- 5. Posterior iliac osteotomy

Complications of the osteotomies were focused on orthopedic or urologic site and documented in 10 series of all reviewed articles dividing in major and so-called minor complications. There was no standard assessment for complications, and instruments like Clavien-Dindo classification were not used in any of these series. As a consequence, the authors themselves classified their complications according their own methodology into different groups. However, it is a general belief that bone and soft tissue of the pelvis must be viewed as a unit in exstrophy, because remodeling of the whole pelvis is assisted by osteotomy during exstrophy closure.⁶⁹ Within the series mostly including different osteotomy types no allocation of complication or outcome and osteotomy type was done.

Six retrospective studies described the primary outcome in the early postoperative period of different osteotomy or abdominal closure techniques in 307 newborn or primary cases. In 172 patients osteotomies were done, whereas in 135 cases pelvis was closed during initial reconstruction without osteotomy. The interesting study from Okubadejo *et al.* actually fitting here, was not included, as these authors were exclusively focussed on patients with complications treated in their center derived from a database of 624 patients "seen in their institute".⁶⁵ They reported 178 exstrophy patients after orthopedic "interventions" with 26 purely orthopedic complications. However, there is no information about the total number of osteotomies performed, no information about exstrophy phenotype, indications, osteotomy type or other clinical or follow-up data of these 624 patients. Additionally, they

excluded primarily all pin site infections of an unknown number, a complication usually included in all the other studies as a minor problem. However, their methodology divided complications very intensively in four groups with a very good methodology, such as bony complication at osteotomy site, neurologic complications at the osteotomy site, complications of traction and deep infection.⁶⁵

In the other included 6 retrospective studies Salter-like osteotomy was applied to 35 cases, Sponsellers' osteotomy to 42 patients, iliac osteotomy to 63 and posterior osteotomy to 32 patients. In these studies about primary outcome 57 complications occurred (33%), including major complications such as dehiscence in 18 cases, deep infection in one case, non-unions of the bones in two cases, leg length asymmetry and sacroiliac pain in one patient each. The majority of complications were reported in the large series from Schaeffer *et al.*, who reported 14 major and 27 minor complications in 63 osteotomies.⁷⁰ Another relevant complication, the femoral nerve palsy was reported in 5 cases out of 3 series. Only one study provided functional follow-up data beside the pure perioperative outcome data and reported persistent pelvic pain in three patients, normal gait and childhood activity in 40 out of 45 post-osteotomy patients.⁷ However, 5 had a persistent waddling-gait and 21 patients followed in a special most probably orthopedic clinic did not have discernible leg-length discrepancy or pelvic instability.⁷¹

Three studies including 83 patients were designed to evaluate the potential of redo osteotomies.^{69,72,73} Two were retrospectively structured, one collected data prospectively.⁷² Patients' age at operation was quite the same with a median of 1.8 and 1.9 years. However, age ranged from a minimum of 0.08 to a maximum of 14.2 years. In these three studies 14 posterior, 18 anterior, 26 vertical combined transverse, 24 Salter osteotomies, and six iliac transverse osteotomies were performed. In the series of Sponseller *et al.*⁷³ no major and minor complications are reported at all. However, the authors report that three patients had transient femoral nerve palsy. In the other two studies 16 complications were noted including three bone non unions, five pin and two plate infections, 4 minor infectious events treated by antibiotics, one pelvic asymmetry and one osteonyelitis. This 19% complication rate was mainly due to infections related to the internal or external fixation material.⁷³ The prospective study examined clinical orthopedic outcome and found no further gait or mobility disturbances according to the initial situation of the patients.⁷² Despite a different methodology, re-do osteotomies per se do not seem to have a higher complication rate than primary case osteotomies.

Studies about long-term sequelae of osteotomies are very important, because there is an ongoing discussion about the imperative necessity of osteotomy in primary exstrophy closure. No indication for osteotomy exists in primary and classical exstrophy cases from a purely orthopedic perspective. In cloacal exstrophy however, individual decisions have to be made. Due to the usually wide and asymmetric diastasis osteotomies are generally needed for initial tension-free abdominal closure.

5.4.4 Long-term issues

There are six studies about long-term outcome issues in this review, including a total of 134 patients, 12 of them without osteotomy were used as controls within follow-up. All studies were clinically based; three of them had control groups.⁷⁴⁻⁷⁶ Three methods were applied to assess long-term orthopedic outcome:

- Questionnaires: modified Nordic musculoskeletal questionnaire (*n*=10 after osteotomy and *n*=8 without osteotomy)⁷⁵; Pediatric Orthopedic Society of North America (POSNA; *n*=8 after osteotomy and *n*=6 without osteotomy)⁷⁴; IOWA hip score (*n*=25).⁷⁷
- 2. X-Rays: parameter symphysis diastasis, signs of degenerative hip disease
- 3. Clinical assessment of range of motion

In these six studies 78 primary and 3 secondary osteotomies were done, including Salter-like osteotomy in 15 cases, ramotomy in 15 patients, Sponseller osteotomy in 1, iliac osteotomy in 12 and posterior osteotomy in 38 patients. Follow-up data was not available, but patients 'age at follow-up' was median 13 years (ranging from 2-63 years) in 5 series, 15 complications were reported, mainly dehiscence in 9 cases, the other 6 cases were only minor complications. The study of Kaar *et al.* found in addition to the well-known abnormalities of the pubic diastasis and the cloacal exstrophy angle in 53% of exstrophy patients at least one other abnormal orthopedic finding, such as hip subluxation, coxa breva, congenital coxa vara, pistol grip deformities, "sagging rope" sign and asymmetric hemipelvis about 24 years after osteotomy.⁷⁸

Satsumas et al. compared the correction and maintenance of the symphysis diastasis after posterior osteotomy (n=6) to anterior or combined osteotomy (n=4).⁷⁹ Patients having undergone posterior osteotomy had a mean pubic approximation of 37.3%, whereas pubic approximation after anterior or combined osteotomy was nearly double as high (62.8%; significant with p < 0.05). In addition, the mean recurrence of separation in pubic diastasis was 90.5% for posterior osteotomy and 41.6% for anterior or combined osteotomy, indicating that anterior approach might be superior in correction of diastasis and maintenance of the closure of the pelvic ring.⁷⁹ In the whole reviewed series, there were five studies comparing the effectiveness of different osteotomy types in respect of long-term symphysis diastasis.^{71,79-82} One study compared symphysis width after different types of osteotomy and without osteotomy in long-term follow-up of approximately 10 years.⁷⁴ Epidemiological data and sex were equally matched in both groups. Three additional studies provided only data on preoperative symphysis width.72,73,83 From all studies provided information about initial symphysis width the gap was median 42 mm with a range from 13 to 140 mm. In the five comparative studies preoperative symphysis width was measured with a median of 41.5 mm (13-75 mm). Postoperative symphysis width after a median follow-up of 8 years was measured with 32.8 mm (10–115 mm). The comparison of symphysis distance after osteotomy versus no osteotomy showed a symphysis diastasis median of 42 mm (range 25-101 mm) following ostetotomy and a symphysis diastasis median of 49 mm (range 24–66 mm) in those patients who did not have osteotomies.¹⁰ Additionally these authors examined urological outcome in these two groups and did not find any significant difference in terms of number of additional continence surgeries required, or in the final continence rate with or without CIC.⁷⁴ Regarding symphysis dissymmetry, it was interesting to note that of the patients with osteotomy only 12.5% had dissymmetry, in the group without osteotomy 50% had pelvis dissymmetry.⁷⁴ Six studies furthermore reported about patients' gait. Half of them stated that all examined patients had normal gait^{73,76,78}; however, 3 studies conceded at least slight impairment with normal gait in 94%, 93% and 87% respectively.^{68,71,84} Patients' complaints reported from interviews showed that mild intermittent low back pain was common.⁷⁸ In a retrospective study patients' complaints

were assessed after 3 types of osteotomy (anterior pubic, anterior supra-acetabular and posterior) and compared to a control population with epispadias who did not get osteotomy with the standardized modified Nordic musculoskeletal questionnaire.⁷⁵

Patients after osteotomy (n=11) had significant more back pain than epispadias patients without osteotomy during the last 12 months (n=8; p<0.024).⁷⁵ The difference was more obvious among men. Although walking performance was about equal, the ability to run was severely impaired in exstrophy patients.⁷⁵ Castagnetti and coworkers used a standardized POSNA questionnaire and found no difference in a study comparing functional results after osteotomy and without osteotomy although patient numbers were low in this series.⁷⁴ The IOWA hip score compared functional outcome in two groups after bilateral iliac (n=10) and bilateral superior pubic ramotomy and found nearly perfect results for both groups.⁷⁷ Regarding the potential association of dysplastic hip changes either as a result of the increasing diastasis or as a primary condition; information was incompletely reported with only two studies providing information. None of their 13 patients had radiographic evidence of degenerative osteoarthritis of the hip.^{76,78} At last there were functional orthopedic examination such as rotational profiles,⁷⁷ measurements of the foot-progression angle or hip external and internal rotation and the Trendelenburg sign.⁷⁸ Most of the reported data were interpreted from the authors as without a relevant pathology as well as of insignificant individual variation.^{77,78}

5.4.5 **Recommendations**

- There is no orthopedic indication for osteotomy in exstrophy. However, the use of osteotomies appears to be associated with a reduction in the incidence of post-operative dehiscence following exstrophy closure in many clinical series. (C)
- 2. Revision osteotomy does not have a higher complication rate per se. The application of a standardized postoperative complication

score after osteotomy using the Baltimore group methodology⁵ would help with standardized assessment. (C)

3. Clinical relevant orthopedic complaints after osteotomy may increase in the long-term, especially in men. However, data about the relevant anatomy like relevant symphysis diastasis or hip morphology predicting the extent or possibility of orthopedic complaints are lacking.(C)

5.5 Exstrophy and Malignancy Concerns

5.5.1 **Methods**

To evaluate malignancy and exstrophy a systematic literature search was performed in Medline from 1969 to 2008 using the following key words: malignancy or neoplasm were searched for exstrophy[All Fields] AND (("fertility"[MeSH Terms] OR "malignancy"[All Fields]) AND ("Issues"[Journal] OR "neoplasms" (with the following limitations: 1) English or German publications, 2) human studies, 3) clinical trials, 4) meta-analyses, 5) review, 6) randomized clinical trial, 7) comparative study, 8) ages birth to 65 years old.

This search resulted in 236 articles within the relevant period until 1969. We excluded 124 articles due to their irrelevance, 12 reviews and 59 case reports due to methodology of the review and 24 further articles and case reports due to language, 16 original articles were included in the review. Among the included studies, 14 were clinical-based, including one that analyzed data from 2 centers.⁸⁵ All 14 studies used retrospectively collected data. Two further studies including the same patient cohort, one from Higuchi *et al.*and one from Husmann *et al.*, were population-based, compared the outcome of patients following enterocystoplasty, (including 38 exstrophy patients) prospectively with a control group over different follow-up periods.^{86,87}

5.5.2 **Recommendations**

- 1. Anatomic reconstruction remains the initial treatment of choice for exstrophy whenever possible given the risk of malignancy when the urinary system is reconstructed with gastrointestinal segments.
- 2. Annual follow-up with an emphasis of electrolyte and tumor surveillance is recommended after enterocystoplasty or urinary diversion. Tumor surveillance should be emphasized beginning 5–10 years following urinary diversion or enterocystoplasty regardless of the underlying indication for the initial reconstruction. Patients with anatomic exstrophy reconstruction have developed tumors in the native bladder and, as such, should have lifelong follow-up.
- 3. Conversion of urinary diversion and removal of the previous reconstruction should be offered to the patient in the setting of dysplasia or localized malignancy.

The studies from Strachan *et al.* and Smeulders *et al.*appear to include the same cohort of patients as well and follow their patients however for a different period. So the actual patients' numbers and cancer index cases may be lower.^{86,88,89} We excluded out of these four studies the two with shorter follow-up each from the review to reduce the chance of double counting malignancies in the whole cohort. In the resulting 14 studies the follow-up of 748 exstrophy patients is reported with a median age of 2.6 years (range 0–15 years) at primary operation. Eight studies did not present data regarding patients' age. Three studies provided information about patients' age at long-term follow-up with a median of 50 years (range 35–69 years). The follow-up period was reported in 10 studies with a median of 15 years (range 8–50; minimum 0.2 years, maximum 69 years). At the time of follow-up, 545 patients in the 14 studies were stated to be alive. In 12 studies 119 deaths were explicitly mentioned, whereas 85 patients out of 8 studies were lost to follow-up. Information was collected during medical chart review in all studies, including telephone interviews in 5 studies and histologic evaluation in two studies and immunhistochemical analysis of the cancer specimen in one study.⁹⁰⁻⁹²

Incorporating the information from case reports and the relevant original articles information about exstrophy and malignancy can be structured in three categories:

- 1. Information about primary cancers in the original exstrophic bladder and possible precursors of this entity or conditions possibly co-occuring with bladder cancers.^{54,85,86,88-91,93}
- 2. Information about cancers related to urinary diversion or augmentation as an incontinence treatment option.
- 3. Information about tumors possibly associated with exstrophy. Last information might be relevant for future follow-up of ectrodactyly-ectodermal dysplasia-clefting syndrome patients during adulthood.

Different types of cancer have been reported in the exstrophic bladder. In two articles, 5 cases of carcinoma are reported including signet-cell-ring carcinoma in one in 1995⁵⁴ and adenocarcinoma in 4 cases in 1988.⁹⁴ The untreated exstrophic bladder has long been recognized to be at increased risk of tumor formation later in life. This remains a relevant concern especially for those born with exstrophy in resource poor countries.⁹⁵⁻⁹⁷ In an additional four articles 16 carcinomas in the exstrophic bladder or bladder remnant are reported, seven of them following bladder augmentation.^{54,86,89,93,98} However, some articles just describe a "mass in the abdomen", a clinical disastrous course and early death, and do not provide differentiated histology. The reported histological subtypes in the literature include adenocarcinoma, squamous cell carcinoma, transitional-cell carcinoma and mixed histology types.

Premalignant lesions have been evaluated. Corica *et al.* described in a two-center study the natural course of cystitis glandularis with intestinal metaplasia after open partial bladder resection or fulguration in a cohort of patients after augmentation, including 35 exstrophy patients.⁸⁵ During a follow-up of 14 years (range 0.9–53 years) no invasive adenocarcinoma of the bladder developed in exstrophic bladders arising from this histologic entity.² Length of follow-up and frequency of evaluation were not described. Two other histologic studies described the incidence of pathologic lesions in exstrophic bladder after biopsy of polyps from the exstrophic bladder, which remained open for various periods till bladder closure. Incidence of cystitis glandularis with intestinal metaplasia was found with a variety of 21%, 36.8%, and 78%.^{85,91} Squamous metaplasia was present in 50% and 55.3%, cystitis glandularis in 36.8% and 70%. However, in these two studies no clinical follow-up or outcome was provided.^{90,91} So, the clinical relevance of these histologic results remains unclear.

In addition, important preconditions like duration of environmental bladder exposure vary widely in the published studies. Until now, there is no consent for a structured bladder surveillance program after functional exstrophy reconstruction with long-term maintenance of the original bladder in use. This might be a result of the fact that bladder cancer has been rarely reported in reconstructed bladders since the reconstruction concept was reestablished in the 1980s under the assumption that the exstrophic bladder remains in use without augmentation. In addition, the clinical course of patients with cancer in bladder remnants after urinary diversion and cystectomy and their additional risk factors are not known. We found only one case from the prospective study control group who had adenocarcinoma of the native exstrophic bladder.⁸⁶ However, other preconditions for cancer development such as urinary infections or other complications as bladder calculi were not reported for that case.

Most long-term data regarding the exstrophy-malignancy topic are available from centers performing or having performed urinary diversion as a primary procedure. The majority of the available patients had either a form of urinary diversion (n=494) or enterocystoplasty (n=158). According the definition of Strachan et al.⁸⁸ and Smeulders et al.⁸⁹ ureterosigmoidostomy confers a high risk for malignancy; 373 patients underwent ureterosigmoidostomy and were reported in five studies exclusively and in three series that included low-risk patients. Due to various reasons such as recurrent infections and cancers, undiversion was necessary after ureterosigmoidostomy in 68 cases (18%). Primary reconstructed patients are reported in seven series, about half of the included patients maintained their bladders in the long-term, reported in two series with a follow-up of a median of 13 years (range 1-65 years) and 14.8 years (range 3-44 years).^{54,85} The other half of the patients underwent secondary urinary diversions. Two articles included exstrophy patients before or after reconstruction. ^{85,91} Two studies include patients after bladder reconstruction and subsequent enterocystoplasty, one of these exclusively after gastrocystoplasty.^{86,98} Patients after enterocystoplasty have been felt to be at low-risk for malignancy since conduits or augmentations do not result in a mixture of urine and feces.^{88,89} However, after gastrocystoplasty 3 carcinomas developed in a group of 29 patients (10%). It remains unclear whether any exstrophy patients were affected with this entity.⁹⁸ These included 2 adenocarcinomas and 1 signet-cell carcinoma, occurring after a median of 12 years (range 11-14).98 In another series, 158 patients underwent enterocystoplasty (n=109 with ileum, n=5 with stomach, and n=44 with colon).

In a prospective population-based study of patients following enterocystoplasty 3 of 38 exstrophy patients died of adenocarcinoma of the bladder 22, 32 and 47 years after augmentation, respectively.⁸⁶ In these studies, the adenocarcinomas of the bladder had an aggressive clinical course with lymphatic or distant metastasis and patient death within a median of 15 months. In the complete series, 11 patients out of 153 patients with vesical dysfunction developed bladder tumors after augmentation. Four of these bladder tumors were urothelial carcinomas and one squamous cell carcinoma having developed in neurogenic bladders. Two additional adenocarcinomas were found in previous posterior valve bladders.⁸⁶

If we include all reported malignancies including the high-risk group (n=373) with mixture of urine and feces together, there were 18 colon carcinomas, 18 adenomas and 3 cases as carcinoma *in situ* described in the literature.^{54,89,92,93,99,100} Latency period for carcinoma *in situ* was reported for 2 cases as 28 and 29 years, respectively.^{90,93} Latency period to invasive colorectal carcinomas was documented in 7 series with a time corridor of median 34 years (range 28.8–42 years). Sixteen carcinomas were reported in bladder remnants, open or augmented exstrophic bladders.^{54,86,89,93,94}

In the explicit low-risk group of patients who have undergone enterocystoplasty or urinary conduit diversion (n=279) 7 carcinomas, 6 adenocarcinomas and one signet-cell carcinoma occurred, additionally 1 bladder carcinoma have been reported^{54,86,89}; 7 series provided information about reasons of death, in 42 patients death was related to malignancy (31%). The risk for malignancy after urinary diversion was estimated by Smeulders *et al.* to be 38% for the high risk group and 3.3 for the low-risk group. Husmann and Higuchi with their groups referred to the same terminology, finding 3 respective 4 bladder cancers in 38 patients who had undergone enterocystoplasty, with a risk of 8 respective 10.5%.⁸⁶⁻⁸⁹ We estimated for the whole reviewed literature the risk in the high risk group with inclusion of adenomas to be 10.5%, in the low-risk group 2.6%.

Information about follow-up programs or plans was available in 6 series. The earliest information from 1986 stated to have included 17% of their patients in a screening program.⁹³ The authors found different levels of awareness for the potential follow-up problems after ureterosigmoidostomy, such as renal function and infection in 100%, metabolic consequences in 48% and the potential cancer development in only 27%.⁹³ Strachan *et al.* stated to have annual colonoscopy since 1980 in their remaining patients after ureterosigmoidostomy.⁸⁸ Stein *et al.* put 32 patients of their initial 102 patients with a follow-up of a median of 18.8 years under a close surveillance, starting 5 years after urinary diversion with annual rectoscopy.⁹⁴ The same group included in 1990 as well 32 patients in the same follow-up protocol.⁹⁸ Pahernik followed 35 patients 10 years after urinary diversion, and followed 16 children with rectoscopy on a regular basis for a follow-up of 11 years (range 8-13 years) without any serious pathological results.¹⁰¹ However, in this series 3 nonspecific inflammatory changes of sigmoid mucosa were reported (19%) and must closely be followed in the long-term over years.¹⁰¹ The long latency period creates a challenge for patient education and motivation in any proposed surveil-lance program.

Associated tumor entities from original articles were affecting the urinary tract, including 1 renal carcinoma, 1 urethral carcinoma and independent 1 carcinoid tumor and 2 ovary tumors in the relevant 14 articles. In addition there are reports in literature including co-occurring 2 Wilms tumors, 1 prostate adenocarcinoma, and 4 testis tumors, described as benign entities such as Leydig cell and Sertoli cell-tumor, a case of seminoma and testicular intraepithelial neoplasia.^{17,89,92,99,102-104}

Many questions remain unanswered. It appears that close annual follow-up after urinary diversion (>30 years), and tumor surveillance starting as early as 5 years after urinary diversion, may be beneficial as there are some reports of malignancy as soon as 10 years after primary diversion. As a screening program, the costs will be significant. Further, in the event of dysplasia or tumor, ureterosig-moidostomy should be changed to other forms of diversion. However, this means that about 30% will

need undiversion in the long-term. If they are benign polyps further surveillance might be sufficient. Due to the significant malignancy risk in urinary diverted patients the preference is still to primary reconstruct the bladder.

In primary reconstructed bladders initial biopsy should be taken at primary reconstruction for histology. Patients having symptoms should be examined by ultrasound and cystoscopy.

There seems to be some evidence for associated tumors in bladder exstrophy-epispadias complex. However during clinical follow-up, doctors may be aware of potential co-occurring malignancy and may therefore have an impact on patients' quality of life.

5.6 Exstrophy and Urinary Tract Infections

5.6.1 **Methods**

To evaluate the urinary infection issues involved with exstrophy a systematic literature search was performed in Medline from 1969 to 2008 using the following key words: exstrophy[All Fields] AND ("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"[All Fields] OR ("urinary"[All Fields]] OR ("urinary"[All Fields]] OR ("urinary"[All Fields]] OR ("urinary"[All Fields]] and with the following limitations: 1) English or German publications, 2) human studies, 3) clinical trials, 4) meta-analyses, 5) review, 6) randomized clinical trial, 7) comparative study, 8) ages birth to 45 years old. During the relevant period till 1969 pub-med showed 54 articles. After reading, 18 were judged as irrelevant. In addition 5 reviews and 6 case reports were excluded due to methodology of the review.

5.6.2 **Recommendations**

- 1. The incidence of UTI appears about 27%, however the long-term risks for the upper tract following UTI remain unclear.
- 2. In settings with known risk factors like co-occurring upper urinary tract obstruction or bladder emptying disturbances, antibiotic prophylaxis, surgical intervention including antireflux procedures are recommended
- 3. After enterocystoplasty, training in proper CIC technique, bladder irrigation programs might be successful to prevent secondary complications like stones, urinary tract obstruction and renal damage.

We identified 103 relevant manuscripts within the relevant period during the initial search. Upon further review, we excluded 69 irrelevant articles, 4 reviews and 6 case reports leaving relevant 24 original articles to review; 23 original articles were designed as retrospective analysis from medical charts; one gathered data prospectively.¹⁰⁵ For the study design, 23 were clinically based. One study was bicentric. In addition to medical chart review, telephone interviews were conducted in 7 studies. Patient populations were heterogeneous for age, gender and reconstruction methods. Criteria to define a UTI varied widely challenging its use as an outcome parameter.

Outcome measurements related to UTI include anatomic and functional risk factors, post-UTI sequelae such as renal function. Some studies included standardized measures such as ultrasound studies of the upper urinary tract, urodynamics (n=18), micturation cystography (i.e micturating cystourethrogram or voiding cystourethrogram) or renal scans. However, as a consequence of retrospective study design it was not clear for instance whether renal scans were performed only after urinary tract infections or during routine follow-up.

The analyzed study population had the following demographics. In total 980 exstrophy patients were assessed, with a median age of 12.3 years (range 0.2–33 years). Fourteen studies did not present data regarding patients' age. Four studies included exclusively adults, as they were primarily addressing sexual function issues. Three of these studies included only female patients (n=77) and one study only male patients (n=30); 176 patients had a median age of 3.2 years (range 0.2–17 years). The only prospective study included 58 patients with a median age of 15 years (range 4–35 years) with over 10 years follow-up with a minimal dropout of 7%.¹⁰⁵ Five studies did not provide information about the gender of the affected exstrophy patients, whereas the others included 491 male and 244 female exstrophy patients, reflecting the well-known male predominance in the male-to-female ratio.¹⁰⁶ A median follow-up of 6.2 years was documented in 18 studies with a range of 1.2 to 13 years; 766 of all recorded patients (78%) underwent primary reconstruction. As a primary intervention or during follow-up continent urinary diversion was performed as an ureterosigmoidostomy in 99 patients, incontinent urinary diversions like ileum or colon conduits had 83 patients and various other urinary diversions had 13 patients; 134 patients performed CIC, 103 via a catheterizable channel according the Mitrofanoff principle (77%) and 215 cases had undergone augmentation.

Urinary tract infection occurred in 261 patients (26.6%). The infection rate varied within the very heterogenous series from 0% to 79% with a median of 22.4%. In four studies including 107 adults UTIs occurred in 22.45% (range 20%–43%). As expected the UTI rate in pregnant women was found to be high, at 43% and 21.5% in two series. In studies solely including patients after reconstruction without augmentation (n=370) urinary tract infections occurred in 56 patients (16%). The infection rate after reconstruction varied from 0 to 42.6% with a median of 19%. After augmentation, the urinary infection rate was between 7 and 65% with a median of 20%. The lowest UTI rate was found in the three studies, where augmentation and CIC was consequently performed in 100%, with a subsequent UTI median rate of 9.4% (7%–22%). A high UTI rate of 56% occurred in a study after reconstruction with emptying problems present in 72%, residual urine in 50%, CIC performed in 33% and augmentation done in 40%.¹⁰⁷ The highest UTI rate of 65% was documented in a study where 46% of the patients needed bladder neck dilatation after bladder neck plasty within the first 3 months and 26% required the same treatment after 3 months.¹⁰⁸ In this series only 22% of the patients performed CIC.¹⁰⁸ One series provided data after reconstruction and primary transurethral CIC.¹⁰⁹

Clean intermittent catheterization was performed in 67% and UTI occurred in 33%.Furthermore an anterior located Mitrofanoff channel seems to have a significant higher risk for UTIs and stone formation than a channel positioned at the posterior bladder wall.¹¹⁰

After primary diversion UTI results varied between 20 and 45% (median 28%). Mesrobian *et al.* presented retrospective data on UTI rate after various types of urinary diversion.¹¹⁰ They saw relevant UTIs after reconstruction in 26%, after incontinent diversion in 45% and continent diversion in 63% within their cohort of 103 patients.⁵⁴

Renal scarring was examined urographically in 2 studies and with renal scans in a further 5 studies.^{54,105,111-113} These studies included 532 patients, who underwent 72 renal scans and an unspecified number of excretory urograms during follow-up; 55 patients out of these 7 studies had renal scarring (9.7%). However, it remained unclear whether the scans were done early after UTI or during follow-up, showing either acute infectious lesions or definitive renal scars, respectively. Fontaine *et al.* monitored prospectively renal function and infection in a group of exstrophy patients, having undergone either bladder augmentation (n=25) or incontinent urinary diversion (n=28). Although symptomatic infections were seen in about 30% of patients, the incidence of renal damage was low. The authors stated, that renal deterioration in the setting of urinary infection was mainly caused by ureteric or renal stones from chronic infection with urea-splitting organisms.¹⁰⁵

Patient education in catheterization techniques and use of long-term prophylactic antibiotics appears to mitigate the risk of UTI.¹⁰⁵ Antibiotic prophylaxis was given in 106 patients. The studies including these patients had a median infection rate of 21.5% (range 9.4%-65%). However it remained unclear whether antibiotic prophylaxis was given due to a high infection rate or as a prophylactic treatment after a surgical intervention. Due to the heterogenity of the study population and the lack of specificity of the timing and definition of UTI, a more detailed analysis was not possible. Nevertheless 3 studies analyzed predisposing conditions for UTI. Braga et al. analyzed the influence of ureterocystoneostomy on UTI rate in a group of 38 primary reconstructed patients, operated at a median age of 3 days (range 1–140 days), after the median follow-up of 2.8 years.¹¹⁴ In the same cohort 15 patients underwent ureterocystoneostomy (39.5%), whereas 23 patients did not have ureterocystoneostomy (60.5%).¹³ UTIs occurred in 12 patients (32%). In the group with ureterocystoneostomy only one patient was affected with febrile UTI compared to 11 patients without ureterocystoneostomy, with 5 having fewer. In the latter group renal scars were detected in 4 patients, which means in 80% of the investigated patients (n=5). Not surprisingly, the UTI rate was statistically significant lower in the group after uretereocystoneostomy than without an antireflux procedure.⁵³ A second study, however, did not find any difference in UTI rate after reconstruction and spontaneously voiding (median follow-up of 12.7 years) with or without uretereocystoneostomy; the infection rate was 20.6% and 22%, respectively.112

In 10 patients (14.5%) renal scaring was detected with renal scans.⁹ The authors found in a multifactorial analysis significant risk factors for renal scarring: one or more febrile urinary tract infections prior to bladder neck reconstruction, the failure to utilize antibiotic prophylaxis following initial bladder closure, the presence and length of presence of residual urine greater than 50 mL following the onset of continence and one or more febrile urinary tract infections following bladder neck reconstruction.¹¹² The same group reported on UTIs after incontinent urinary diversion such as non-refluxing colon conduit in a cohort of 25 patients with a mean age of 0.8 years (range 0–6 years) after a 12.7 year follow-up. Although they found bacteriologic colonization of the conduits in 96% of all cases, significant clinically symptomatic UTIs with fewer occurred in only 7 patients (28%) with renal scaring in 5 of these cases (71%) High risk factor for symptomatic UTI was co-occurring urinary obstruction most probably after antireflux procedure in this conduits, which was detected in their patients with UTI in 70%.¹¹¹

5.7 Renal Function and Exstrophy

5.7.1 Methods

To evaluate renal function and exstrophy a systematic literature search was performed in Medline from 1969 to 2008 using the following key words: exstrophy[All Fields] AND ("renal function"[MeSH Terms] OR ("kidney"[All Fields] AND "function"[All Fields] OR "renal function All Fields] OR ("kidney" [All Fields] AND "function" OR "kidney function"[All Fields]) and with the following limitations: 1) English or German publications, 2) human studies, 3) clinical trials, 4) meta-analyses, 5.) review, 6) randomized clinical trial, 7) comparative study, 8) ages birth to 45 years old. On the initial review, we identified 203 articles. On further review 73 were felt to be relevant and included 5 reviews, 2 case reports, and 43 original articles, 13 articles were excluded secondary to language. These articles included 24 that described renal function after functional reconstruction and 21 series that described renal function or augmentation.

At birth, the majority of patients with exstrophy have normal renal function. The natural history of both treated and untreated exstrophy carries an increased risk of renal damage secondary to urinary infections and lower outlet obstruction.

Renal functional outcomes varied widely throughout these series. Several centers presented clinical series of exstrophy patients that claimed no adverse impact on renal function on follow-up. The conclusions of many of these studies were limited by short follow-up, significant patient drop-out during follow-up, selection bias, incomplete patient demographic data, and/or a lack of renal function data to confirm their assertions.¹¹⁵⁻¹¹⁷ In one study, the available aggregate data suggested renal impairment among some patients although the authors stated that the patients in the series had normal renal function.¹¹⁸ Other studies have documented adverse impact on renal function as documented by new hydronephrosis, elevated serum creatinine, or renal damage as documented by dimercaptosuccinic acid (DMSA) renal scan. In these studies, the subset of patients affected is in the minority. For instance, Gargollo and colleagues noted 6 of 32 patients had renal scars by DMSA scan and 7 patients had hydronephrosis.¹¹⁹ Similar findings were noted by El Sherbiny in a series of patients repaired with a complete exstrophy repair approach.¹²⁰ A range of renal function outcomes was noted whether an anatomic reconstructive approach was used or urinary diversion via ureterosigmoidostomy (USO) or one of its variants.¹²¹ Hafez reported normal renal function in a patient group that had undergone urinary diversion.¹²² Meyrat and colleagues noted 34% of patients presented with one or more episodes of pyelonephritis. Intravenous pyelograms showed improved or unchanged urinary tract dilatation in 45% of kidneys and moderate and severe dilatation in 55% of the patients in their

series of long-term follow-up after USO. Inulin clearance remained in the normal range in 4 out of 6 patients followed. Renal function assessed by means of renal scintigraphy remained unchanged in 61% of kidneys, slightly decreased in 22% and severely in 17%.¹²³ Long-term studies of exstrophy patients into adulthood consistently identified a subset of patients who demonstrated renal damage.

Other series have identified risk factors for renal scarring. Husmann and co-authors noted that in a series of 68 exstrophy patients who underwent staged exstrophy reconstruction, 14.7% developed renal scarring. The authors found on multifactorial analysis that one or more febrile urinary tract infections prior to bladder neck reconstruction, failure to utilize antibiotic prophylaxis following initial bladder closure elevated urinary residuals greater than 50 mL, and one or more febrile urinary tract infections following bladder neck reconstruction were all factors that were significantly related to an increased risk of renal scarring.¹¹²

5.7.2 **Recommendations**

- 1. Female exstrophy patients may require vaginal reconstruction after the initial exstrophy closure. They are at higher risk than the general population of uterine and vaginal prolapse regardless of a history of pregnancy. (C)
- 2. Female exstrophy patients who achieve a pregnancy should be considered a high risk pregnancy given their underlying congenital anomaly. (C)
- 3. Male exstrophy patients have decreased fertility. Early evaluation and use of assisted reproductive techniques should be considered and offered. (C)
- 4. Both male and femal exstrophy patients should be offered psychological support throughout their development to address concerns regarding genital appearance and sexual function. (C)
- 5. Primary anatomic reconstruction should be attempted when possible. (C)
- 6. Bladder capacity should be assessed to determine optimal options for continence if the patient remains incontinent. (C)
- 7. Urinary diversion can be considered in the setting of failed exstrophy repair or for patients in a resource-poor region. (C)

- 8. There is no orthopedic indication for osteotomy in exstrophy. However, the use of osteotomies appears to be associated with a reduction in the incidence of post-operative dehiscence following exstrophy closure in many clinical series. (C)
- 9. Revision osteotomy does not have a higher complication rate per se. The application of a standardized postoperative complication score after osteotomy using the Baltimore group methodology would help with standardized assessment.65
- 10. Clinical relevant orthopedic complaints after osteotomy may increase in the long-term, especially in men. However, data about the relevant anatomy like relevant symphysis diastasis or hip morphology predicting the extent or possibility of orthopedic complaints are lacking. (C)
- 11. Anatomic reconstruction remains the initial treatment of choice for exstrophy whenever possible given the risk of malignancy when the urinary system is reconstructed with gastrointestinal segments. (C)
- 12. Annual follow-up with an emphasis of electrolyte and tumor surveillance is recommended after enterocystoplasty or urinary diversion. Tumor surveillance should be emphasized beginning 5-10 years following urinary diversion or enterocystoplasty regardless of the underlying indication for the initial reconstruction. Patients with anatomic exstrophy reconstruction have developed tumors in the native bladder and, as such, should have lifelong follow-up. (C)
- 13. Conversion of urinary diversion and removal of the previous reconstruction should be offered to the patient in the setting of dysplasia or localized malignancy. (C)
- 14. The incidence of UTI appears about 27%; however, the long-term risks for the upper tract following UTI remain unclear. (C)
- 15. In settings with known risk factors like co-occurring upper urinary tract obstruction or bladder emptying disturbances, antibiotic prophylaxis, surgical intervention including antireflux procedures are recommended. (C)
- 16. After enterocystoplasty training in proper CIC technique, bladder irrigation programs might be successful to prevent secondary complications like stones, urinary tract obstruction, and renal damage. (C)

5.8 **References**

- 1. Gearhart JP. The exstrophy-epispadias complex in the new millennium--science, practice and policy. J Urol, 1999. 162(4):1421–1423.
- 2. Lattimer JK, Smith MJ. Exstrophy closure: a followup on 70 cases. J Urol. 1966;95(3):356-359.
- 3. Engel RM. Exstrophy of the bladder and associated anomalies. Birth Defects Orig Artic Ser. 1974;10(4):146–149.
- 4. Stein R, et al. The fate of the adult exstrophy patient. J Urol. 1994;152(5 Pt 1):1413-1416.
- 5. Stein R, *et al.* Operative reconstruction of the external and internal genitalia in female patients with bladder exstrophy or incontinent epispadias. J Urol. 1995;154(3):1002–1007.
- Stein R, et al. Social integration, sexual behavior and fertility in patients with bladder exstrophy--a long-term follow up. Eur J Pediatr. 1996;155(8):678–683.
- Stein R, et al. Strategies for reconstruction after unsuccessful or unsatisfactory primary treatment of patients with bladder exstrophy or incontinent epispadias. J Urol. 1999;161(6):1934–1941.
- Stein R, et al. Management of bladder exstrophy and incontinent epispadias: 25 years of experience with urinary diversion. Arch Esp Urol. 1997;50(1):91–102; discussion 102–104.
- 9. Stein R, *et al.* Treatment of patients with bladder exstrophy or incontinent epispadias. A long-term follow-up. Eur Urol. 1997;31(1):58-64.
- 10. Woodhouse CR, Hinsch R. The anatomy and reconstruction of the adult female genitalia in classical exstrophy. Br J Urol. 1997;79(4):618-622.
- 11. Burbige KA, et al. Pregnancy and sexual function in women with bladder exstrophy. Urology. 1986;28(1):12–14.
- 12. Meyer KF, et al. The exstrophy-epispadias complex: is aesthetic appearance important? BJU Int. 2004;93(7):1062–1068.
- Reiner WG. Psychosexual development in genetic males assigned female: the cloacal exstrophy experience. Child Adolesc Psychiatr Clin N Am. 2004;13(3):657–674, ix.
- 14. Ebert A, *et al.* Psychosocial and psychosexual development in childhood and adolescence within the exstrophy-epispadias complex. J Urol. 2005;174(3):1094–1098.
- Ebert AK, et al. Long-term follow-up of male patients after reconstruction of the bladder-exstrophy-epispadias complex: psychosocial status, continence, renal and genital function. J Pediatr Urol. 2010;6(1):6–10.
- 16. Wittmeyer V, et al. Quality of life in adults with bladder exstrophy-epispadias complex. J Urol. 2010;184(6):2389–2394.
- 17. Baird, A.D., *et al.* Coping with bladder exstrophy: diverse results from early attempts at functional urinary tract surgery. BJU Int, 2004;93(9):1303–1308.
- Deans R, et al. Reproductive outcomes in women with classic bladder exstrophy: an observational cross-sectional study. Am J Obstet Gynecol, 2012;206:496.e1–e6.
- 19. Greenwell TJ, et al. Pregnancy after lower urinary tract reconstruction for congenital abnormalities. BJU Int. 2003;92(7):773–777.
- Blakeley CR, Mills WG. The obstetric and gynaecological complications of bladder exstrophy and epispadias. Br J Obstet Gynaecol. 1981;88(2):167–173.
- 21. Stanton SL. Gynecologic complications of epispadias and bladder exstrophy. Am J Obstet Gynecol. 1974;119(6):749-754.
- 22. Woodhouse CR. The sexual and reproductive consequences of congenital genitourinary anomalies. J Urol. 1994;152(2 pt 2):645-651.
- Feitz WF, et al. Outcome analysis of the psychosexual and socioeconomical development of adult patients born with bladder exstrophy. J Urol. 1994;152(5 pt 1):1417–1419.
- Mathews RI, Gan M, Gearhart JP. Urogynaecological and obstetric issues in women with the exstrophy-epispadias complex. BJU Int, 2003;91(9):845–849.

- Giron AM, et al. Bladder exstrophy: reconstructed female patients achieving normal pregnancy and delivering normal babies. Int Braz J Urol. 2011;37(5):605–610.
- 26. Nakhal RS, et al. Genital prolapse in adult women with classical bladder exstrophy. Int Urogynecol J. 2012;23:1201–1205.
- 27. Ben-Chaim J, et al. The outcome of patients with classic bladder exstrophy in adult life. J Urol. 1996;155(4):1251–1252.
- 28. Krisilof M, et al. Pregnancy in women with bladder exstrophy. J Urol. 1978;119(4):478-479.
- 29. Anusionwu I, et al. Is pelvic osteotomy associated with lower risk of pelvic organ prolapse in postpubertal females with classic bladder exstrophy? J Urol. 2012;188(6):2343–2346.
- 30. Salem HK, Eisa M, Long-term follow-up (18-35 years) of male patients with history of bladder exstrophy (BE) repair in childhood: erectile function and fertility potential outcome. J Sex Med. 2011;9(5):1466–1472.
- 31. Hanna MK, Williams DI. Genital function in males with vesical exstrophy and epispadias. Br J Urol. 1972;44(2):169–174.
- 32. Ebert AK, *et al.* Genital and reproductive function in males after functional reconstruction of the exstrophy-epispadias complexlong-term results. Urology, 2008;72(3):566–569; discussion 569–570.
- 33. Nerli RB, et al. Bladder exstrophy in adulthood. Indian J Urol, 2008;24(2):164–168.
- 34. Avolio L, *et al.* The long-term outcome in men with exstrophy/epispadias: sexual function and social integration. J Urol, 1996;156(2 pt 2):822–825.
- 35. Hafez AT, Helmy T. Complete penile disassembly for epispadias repair in postpubertal patients. Urology. 2011;78(6):1407–1410.
- 36. Woodhouse CR. Prospects for fertility in patients born with genitourinary anomalies. J Urol. 2001;165(6 pt 2):2354–2360.
- 37. Woodhouse CR. Sexual function in boys born with exstrophy, myelomeningocele, and micropenis. Urology. 1998;52(1):3–11.
- Lattimer JK, MacFarlane MT, Puchner PJ. Male exstrophy patients: a preliminary report on the reproductive capability. Trans Am Assoc Genitourin Surg. 1978;70:42–44.
- 39. Castagnetti M, et al. Sexual function in men born with classic bladder exstrophy: a norm related study. JUrol. 2010;183(3):1118–1122.
- Reiner WG, Gearhart JP, Jeffs R, Psychosexual dysfunction in males with genital anomalies: late adolescence, Tanner stages IV to VI. J Am Acad Child Adolesc Psychiatry, 1999;38(7):865–872.
- Diseth TH, et al. Somatic function, mental health and psychosocial functioning in 22 adolescents with bladder exstrophy and epispadias. J Urol. 1998;159(5):1684–1689; discussion 1689–1690.
- 42. Lloyd JC, *et al.* How dry is dry? A review of definitions of continence in the contemporary exstrophy/epispadias literature. J Urol. 2012;188(5):1900–1904.
- 43. Gupta AD, et al. Examining long-term outcomes of bladder exstrophy: a 20-year follow-up. BJU Int. 2014;113(1):137–141.
- Shnorhavorian M, et al. Long-term followup of complete primary repair of exstrophy: the Seattle experience. J Urol. 2008;180(4 suppl):1615–1619; discussion 1619–1620.
- Gargollo P, et al. Bladder neck reconstruction is often necessary after complete primary repair of exstrophy. J Urol. 2011;185(6 suppl):2563–2571.
- 46. Borer JG, *et al.* Early outcome following complete primary repair of bladder exstrophy in the newborn. J Urol. 2005;174(4 pt 2):1674–1678; discussion 1678–1679.
- Jarzebowski AC, et al. The Kelly technique of bladder exstrophy repair: continence, cosmesis and pelvic organ prolapse outcomes. J Urol. 2009;182(4 suppl):1802–1806.
- Berrettini A, Castagnetti M, Rigamonti W. Radical soft tissue mobilization and reconstruction (Kelly procedure) for bladder extrophy [correction of exstrophy] repair in males: initial experience with nine cases. Pediatr Surg Int. 2009;25(5):427–431.
- Hollowell JG, et al. Evaluation and treatment of incontinence after bladder neck reconstruction in exstrophy and epispadias. Br J Urol. 1993;71(6):743–749.
- Jones JA, Mitchell ME, Rink RC, Improved results using a modification of the Young-Dees-Leadbetter bladder neck repair. Br J Urol. 1993;71(5):555–561.
- 51. Woodhouse CR, Redgrave NG, Late failure of the reconstructed exstrophy bladder. Br J Urol. 1996;77(4):590-592.

- Baird AD, Nelson CP, Gearhart JP. Modern staged repair of bladder exstrophy: a contemporary series. J Pediatr Urol. 2007;3(4):311–315.
- Mollard P, Mouriquand PD, Buttin X. Urinary continence after reconstruction of classical bladder exstrophy (73 cases). Br J Urol. 1994;73(3):298–302.
- 54. Mesrobian HG, Kelalis PP, Kramer SA. Long-term followup of 103 patients with bladder exstrophy. J Urol. 1988;139(4):719–722.
- 55. Husmann DA, McLorie GA, Churchill BM. Closure of the exstrophic bladder: an evaluation of the factors leading to its success and its importance on urinary continence. J Urol. 1989;142(2 pt 2):522–524; discussion 542–543.
- 56. McMahon DR, et al. Vesical neck reconstruction in patients with the exstrophy-epispadias complex. J Urol. 1996;155(4):1411–1413.
- 57. Gearhart JP, et al. Prostate size and configuration in adults with bladder exstrophy. J Urol, 1993;149(2):308-310.
- 58. Fisch M, Wammack R, Hohenfellner R. The sigma rectum pouch (Mainz pouch II). World J Urol. 1996;14(2):68–72.
- 59. Hollowell JG, et al. Lower urinary tract function after exstrophy closure. Pediatr Nephrol. 1992;6(5):428-432.
- 60. Nisonson I, Lattimer JK. How well can the exstrophied bladder work? J Urol. 1972;107(4):664-666.
- 61. Hohenfellner R, Stein R, Primary urinary diversion in patients with bladder exstrophy. Urology. 1996;48(6):828-830.
- 62. Surer I, et al. Continent urinary diversion and the exstrophy-epispadias complex. J Urol. 2003;169(3):1102–1105.
- 63. Tacciuoli M, Laurenti C, Racheli T. Sixteen years' experience with the Heitz Boyer-Hovelacque procedure for exstrophy of the bladder. Br J Urol. 1977;49(5):385–390.
- 64. Ben-Chaim J, et al. Bladder exstrophy from childhood into adult life. J R Soc Med. 1996;89(1):39P-46P.
- 65. Okubadejo GO, Sponseller PD, Gearhart JP, Complications in orthopedic management of exstrophy. J Pediatr Orthop. 2003;23(4):522–528.
- 66. Lascombes P, *et al.* Anatomic basis for the orthopedic treatment of bladder exstrophy: anatomic study of the sacrosciatic ligaments in the newborn. Surg Radiol Anat. 1988;10(2):97–100.
- Loder RT, Dayioglu MM. Association of congenital vertebral malformations with bladder and cloacal exstrophy. J Pediatr Orthop. 1990;10(3):389–393.
- 68. Sponseller PD, et al. The anatomy of the pelvis in the exstrophy complex. J Bone Joint Surg Am. 1995;77(2):177-189.
- 69. Nelson CP, *et al.* Repeat pelvic osteotomy in patients with failed closure of bladder exstrophy: applications and outcomes. J Pediatr Surg. 2006;41(6):1109–1112.
- Schaeffer AJ, et al. Complications of primary closure of classic bladder exstrophy. J Urol, 2008;180(4 suppl):1671–1674; discussion 1674.
- Jones D, Parkinson S, Hosalkar HS. Oblique pelvic osteotomy in the exstrophy/epispadias complex. J Bone Joint Surg Br. 2006;88(6):799–806.
- 72. Schartz RB, et al. Repeat pelvic osteotomy in cloacal exstrophy: applications and outcomes. J Pediatr Urol. 2007;3(5):398-403.
- Sponseller PD, Gearhart JP, Jeffs RD. Anterior innominate osteotomies for failure or late closure of bladder exstrophy. J Urol. 1991;146(1):137–140.
- 74. Castagnetti M, *et al.* Comparison of musculoskeletal and urological functional outcomes in patients with bladder exstrophy undergoing repair with and without osteotomy. Pediatr Surg Int. 2008;24(6):689–693.
- Suominen JS, Helenius I, Taskinen S, Long-term orthopedic outcomes in patients with epispadias and bladder exstrophy. J Pediatr Surg. 2012;47(10):1821–1824.
- 76. Kantor R, Salai M, Ganel A. Orthopaedic long term aspects of bladder exstrophy. Clin Orthop Relat Res. 1997(335):240-245.
- 77. Schmidt AH, *et al.* Pelvic osteotomy for bladder exstrophy. J Pediatr Orthop. 1993;13(2):214–219.
- Kaar SG, et al. Association of bladder exstrophy with congenital pathology of the hip and lumbosacral spine: a long-term follow-up study of 13 patients. J Pediatr Orthop. 2002;22(1):62–66.

- 79. Satsuma S, *et al.* Comparison of posterior and anterior pelvic osteotomy for bladder exstrophy complex. J Pediatr Orthop B. 2006;15(2):141–146.
- 80. Frey P. Bilateral anterior pubic osteotomy in bladder exstrophy closure. J Urol. 1996;156(2 pt 2):812-815.
- 81. Romanus B. Pelvic osteotomy and symphysis reconstruction in bladder exstrophy: Early (2-6 years) results with a new (Double Door) symphysis reconstruction. J Pediatr Urol. 2006;2(4):294–298.
- Frey P, Cohen SJ. Anterior pelvic osteotomy. A new operative technique facilitating primary bladder exstrophy closure. Br J Urol. 1989;64(6):641–643.
- 83. Sponseller PD, et al. Anterior innominate osteotomy in repair of bladder exstrophy. J Bone Joint Surg Am. 2001;83-A(2):184–193.
- Gugenheim JJ, et al. Bilateral posterior pelvic resection osteotomies in patients with exstrophy of the bladder. Clin Orthop Relat Res. 1999(364):70–75.
- Corica FA, et al. Intestinal metaplasia is not a strong risk factor for bladder cancer: study of 53 cases with long-term follow-up. Urology. 1997;50(3):427–431.
- 86. Higuchi TT, et al. Augmentation cystoplasty and risk of neoplasia: fact, fiction and controversy. J Urol. 2010;184(6):2492–2496.
- Husmann DA, Rathbun SR, Long-term follow up of enteric bladder augmentations: the risk for malignancy. J Pediatr Urol. 2008;4(5):381–385; discussion 386.
- Strachan JR, Woodhouse CR. Malignancy following ureterosigmoidostomy in patients with exstrophy. Br J Surg. 1991;78(10):1216–1218.
- 89. Smeulders N, Woodhouse CR. Neoplasia in adult exstrophy patients. BJU Int. 2001;87(7):623-628.
- 90. Fan R, et al. Exstrophy polyp is a unique pathology entity. Pediatr Dev Pathol. 2012;15(6):471-477.
- 91. Novak TE, et al. Polyps in the exstrophic bladder. A cause for concern? J Urol. 2005;174(4 Pt 2):1522–1526; discussion 1526.
- 92. PetterssonL, etal. Halfcentury of followup after ureterosigmoidostomy performed in early childhood. J Urol. 2013;189(5):1870–1875.
- 93. Zabbo A, Kay R. Ureterosigmoidostomy and bladder exstrophy: a long-term followup. J Urol. 1986;136(2):396-398.
- 94. Stein R, et al. Urinary diversion in bladder exstrophy and incontinent epispadias: 25 years of experience. J Urol. 1995;154(3):1177–1181.
- 95. Rieder JM, et al. Primary squamous cell carcinoma in unreconstructed exstrophic bladder. Urology, 2006;67(1):199.
- 96. Bansal P, *et al.* Squamous cell carcinoma in exstrophic unreconstructed urinary bladder in an adult. Saudi J Kidney Dis Transpl. 2012;23(1):122–124.
- 97. Bango Garcia V, et al. [Primary bladder adenocarcinoma in unreconstructed exstrophic bladder]. Actas Urol Esp, 2009;33(2):197–199.
- 98. Castellan M, et al. Complications after use of gastric segments for lower urinary tract reconstruction. J Urol. 2012;187(5):1823-1827.
- Gobet R, et al. Long-term followup (37 to 69 years) in patients with bladder exstrophy treated with ureterosigmoidostomy: psychosocial and psychosexual outcomes. J Urol. 2009;182(4 suppl):1819–1823.
- 100. Stockle M, *et al.* Ureterosigmoidostomy: an outdated approach to bladder exstrophy? J Urol. 1990;143(4):770–774; discussion 774–775.
- 101. Pahernik S, et al. Rectosigmoid pouch (Mainz Pouch II) in children. J Urol. 2006;175(1):284-287.
- 102. Candia A, Zegel HG. The occurrence of Wilms tumor in 2 patients with exstrophy of the bladder. J Urol. 1982;128(3):589-590.
- Berkowitz J, Carter HB, Gearhart JP, Prostate cancer in patients with the bladder exstrophy-epispadias complex: insights and outcomes. Urology. 2008;71(6):1064–1066.
- 104. Ebert AK, et al. Testicular tumors in patients with exstrophy-epispadias complex. J Urol. 2012;188(4):1300–1305.
- 105. Fontaine E, Leaver R, Woodhouse CR. The effect of intestinal urinary reservoirs on renal function: a 10-year follow-up. BJU Int. 2000;86(3):195–198.
- 106. Ebert AK, et al. The exstrophy-epispadias complex. Orphanet J Rare Dis. 2009;4:23.
- 107. Yerkes EB, et al. How well do patients with exstrophy actually void? J Urol. 2000;164(3 Pt 2):1044–1047.

- 108. Mouriquand PD, *et al.* Long-term results of bladder neck reconstruction for incontinence in children with classical bladder exstrophy or incontinent epispadias. BJU Int. 2003;92(9):997–1001; discussion 1002.
- van Leeuwen MA, et al. Primary repair of bladder exstrophy followed by clean intermittent catheterization: outcome of 15 years' experience. Urology. 2006;67(2):394–398; discussion 398–399.
- 110. Berkowitz J, et al. Mitrofanoff continent catheterizable conduits: top down or bottom up? J Pediatr Urol. 2009;5(2):122-5.
- 111. Husmann DA, McLorie GA, Churchill BM. Nonrefluxing colonic conduits: a long-term life-table analysis. J Urol. 1989;142(5):1201-1203.
- 112. Husmann DA, McLorie GA, Churchill BM. Factors predisposing to renal scarring: following staged reconstruction of classical bladder exstrophy. J Pediatr Surg. 1990;25(5):500–504.
- 113. Bhatnagar V, et al. Augmentation colocystoplasty in bladder exstrophy. Pediatr Surg Int. 2002;18(1):43-49.
- 114. Braga LH, et al. Bilateral ureteral reimplantation at primary bladder exstrophy closure. J Urol. 2010;183(6):2337-2341.
- 115. Kanojia RP, et al. Quantified outcome for patients with bladder exstrophy. J Pediatr Urol. 2013;9(3):298-302.
- Schaeffer AJ, et al. Preservation of renal function in the modern staged repair of classic bladder exstrophy. J Pediatr Urol. 2013;9(2):169–173.
- 117. Novak TE, *et al.* Bladder neck transection for intractable pediatric urinary incontinence. J Urol. 2009;181(1):310–314; discussion 314.
- 118. Baradaran N, *et al.* Urinary diversion in early childhood: indications and outcomes in the exstrophy patients. Urology. 2012;80(1):191–195.
- 119. Gargollo PC, *et al.* Prospective followup in patients after complete primary repair of bladder exstrophy. J Urol. 2008;180(4 suppl):1665–1670; discussion 1670.
- El-Sherbiny MT, Hafez AT, Ghoneim MA. Complete repair of exstrophy: further experience with neonates and children after failed initial closure. J Urol. 2002;168(4 Pt 2):1692–1694; discussion 1694.
- 121. Husmann DA, McLorie GA, Churchill BM. A comparison of renal function in the exstrophy patient treated with staged reconstruction versus urinary diversion. J Urol. 1988;140(5 pt 2):1204–1206.
- 122. Hafez AT, *et al.* Long-term outcome analysis of low pressure rectal reservoirs in 33 children with bladder exstrophy. J Urol, 2001;165(6 pt 2):2414–2417.
- 123. Meyrat BJ, Berger D, Stucky P. Ureterosigmoidostomy: a long-term follow-up of 15 patients with urinary diversion. Eur J Pediatr Surg. 1991;1(3):172–176.



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6.1 Introduction

Cloacal exstrophy is a very complex anomaly that involves multiple organ systems, including the urinary, gastrointestinal, neurological, and orthopedic. Significant improvement in surgical management over the last 40 years has led to most patients surviving into adulthood.^{1,2} In an effort to determine current advances in embryology, epidemiology, evaluation, and management, a review of the recent literature was conducted.

6.2 Methods

To review the evaluation and management of cloacal exstrophy, a systematic literature search was performed in Medline from 1969 to 2013 using the following key words: cloacal and OEIS were searched for exstrophy [All Fields] AND (("cloacal"[MeSH Terms] OR "cloacal"[All Fields]) AND ("Issues"[Journal] OR "Issues (St Louis Mo)"[Journal] OR "issues"[All Fields])) as well as exstrophy[All Fields] AND (genital[All Fields] AND ("physiology"[Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms] OR "function"[All Fields])) and exstrophy[All Fields] AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) and exstrophy[All Fields] AND ("sexual behavior"[MeSH Terms] OR ("sexual"[All Fields] AND (behavior"[All Fields]) OR "sexual behavior"[All Fields] OR "function"[All Fields] OR "sexual"[All Fields]) and exstrophy[All Fields] OR "function"[All Fields] OR "function"[All Fields]] OR "sexual behavior"[MeSH Terms] OR ("sexual"[All Fields] AND (behavior"[All Fields]) OR "sexual behavior"[All Fields] OR "function"[All Fields]] OR "physiology"[All Fields]] OR "physiology"[All Fields]] OR "physiology"[All Fields]] OR "sexual behavior"[All Fields] OR "sexual"[All Fields]] AND ("physiology"[Subheading]] OR "physiology"[All Fields]] OR "sexual behavior"[All Fields]] OR "function"[All Fields]] OR "physiology"[All Fields]] OR "function"[All Fields]] OR "sexual"[All Fields]] OR "physiology"[All Fields]] OR "physiology"[All Fields]] OR "function"[All Fields]] OR "sexual"[All Fields]] OR "physiology"[All Fields]] OR "function"[All Fields]]) with the following limitations: 1) English or German publications, 2) human studies, 3) clinical trials, 4) meta-analyses, 5) reviews, 6) randomized clinical trials, 7) comparative studies, 8) ages birth to 65 years old.

During the relevant period from 1969 to 2013, we identified 129 articles, irrespective of patients' gender, related to cloacal exstrophy. Of these, 58 articles were excluded, because they did not meet inclusion criteria for this section of the review. From the remaining 71 articles, seven nonsystematic reviews, 13 case reports, and eight articles were excluded due to language, leaving 43 articles for analysis.

6.3 **Prenatal Evaluation**

Ultrasound evaluation has been the primary modality for the prenatal diagnosis of cloacal exstrophy.^{3,4} Despite being able to accurately diagnose cloacal exstrophy prenatally in the vast majority of cases, in some, confirmation of diagnosis remains challenging. Recently, fetal magnetic resonance imaging has been used successfully to determine or confirm the diagnosis of cloacal exstrophy.^{5,6} This permits prenatal counseling of the expectant parents, as well as preparation for delivery at a tertiary care centre, where specialty care for the mother and newborn can be available.

FIGURE 6-1 Newborn with cloacal exstrophy.



FIGURE 6-2 Diagram of newborn with cloacal exstrophy.

BP: bladder plate C: cecal plate CB: corporal bodies HG: hindgut IL: ileum O: omphalocele UO: ureteral orifice



6.4 Epidemiology

Cloacal exstrophy is most likely etiologically heterogeneous.⁷ Evaluation of a database that included 24 countries found that the incidence of cloacal exstrophy was 1 in 131,579 births, with higher prevalence in Wales and much lower prevalence in South America. Preconception maternal exposure to smoking was more common in patients with cloacal exstrophy than in those with epispadias/classic exstrophy.⁸ Mothers carrying fetuses with cloacal exstrophy were more compliant with folic acid supplementation, indicating that this was not preventive for the spinal defects noted with cloacal exstrophy. Prenatal use of clomiphene citrate has been cited as a potential risk factor for the development of cloacal exstrophy.⁹ Additionally, maternal smoking and first trimester radiation are associated with an increased incidence of cloacal exstrophy.¹⁰

6.5 **Spectrum of Anomalies**

Cloacal exstrophy comprises a spectrum of anomalies in multiple systems, as noted in **Figures 6-1** and **6-2**. There is significant variability in the anatomic presentation of cloacal exstrophy, with many children having varying degrees of skeletal, urological, gastrointestinal, and neurological anomalies.

Management for children with cloacal exstrophy therefore must be individualized to the encountered anatomic anomalies. While generalization of management is difficult, some general principles are crucial for successful outcomes. Today, most management strategies are directed to improving the quality of life because survival, with the introduction of intensive care management and total parenteral nutrition, should be high in most regions of the world.¹¹

6.6 Initial Management

The immediate management of the infant with cloacal exstrophy is directed to medical stabilization, evaluation of the anatomy, and counseling for the family. These patients present a significant medical challenge, and in resource-poor regions of the world, mortality is still more than 50%.¹² Neonatal death is typically due to overwhelming infection, with the underlying cause ranging from malnutrition and dehydration, urinary or fecal leak, meningitis, and metabolic acidosis.²

Once medically stable, management of the neurospinal defect and commonly associated omphalocele takes precedence over urologic and gastrointestinal interventions. Myelomeningocele occurs in 29% to 75% of these patients, with up to 100% having some form of neural tube abnormality.² A team approach to management is ideal, with involvement of the pediatric surgeon, pediatric neurosurgeon, pediatric orthopedist, pediatric urologist, pediatrician, endocrinologist, and pediatric psychologist or psychiatrist.¹¹ Following neurosurgical management, the next steps are management of the omphalocele, and urologic and gastrointestinal reconstruction with abdominal wall closure.

6.6.1 Intestinal reconstruction

Initial surgical reconstruction consists of fecal diversion to an ostomy with preservation and tubularization of the hindgut remnant as a mucus fistula in continuity with the rest of the intestine. Preservation of the hindgut remnant, and later inclusion into the intestinal tract to provide greater absorptive surface area, has emerged as an important aspect for intestinal reconstruction that reduces the risk for metabolic acidosis and dehydration that occur with ileostomy in patients with cloacal exstrophy.^{11,13} If during later reconstruction, the hindgut remnant is not used in the gastrointestinal tract, it can be used for vaginal reconstruction or enterocystoplasty.²

Long-term bowel management¹⁴ is dependent on the length of available bowel. Some children are candidates for eventual pull-through procedures. However, in children with short gut and poor absorption, long-term stomas are the only viable option. Most patients will have a nonorthotopic ostomy or a perineal colostomy of variable continence.¹⁵ Continent fecal reservoirs of the Kock type have been reported.^{14,16} The choice to proceed with an anorectoplasty is impacted by several factors: 1) the ability to solidify stool, 2) sphincter function and the neuromuscular status of the pelvic floor, 3) walking ability, and 4) parental expectations. Initial clinical outcomes have been reported to be as high as 76% fecal control, but only with daily washouts or enemas.¹⁷ Variation in the use of this technique ranges widely, with just 10% of children undergoing anorectoplasty to other series reporting routine use of a pull-through with a 70% fecal continence rate.^{18,19}

6.6.2 **Urinary and abdominal wall reconstruction**

Initial reconstruction at the time of intestinal diversion includes abdominal wall closure and may require osteotomy and pelvic fixation.¹¹ Additionally, at the time of closure, genital reconstruction is performed to approximate the phallic halves in male patients and to reconstruct the introitus in female patients. Inguinal hernias, if present, are repaired at the same time. The use of osteotomy at this time is associated with a significant reduction in complications.²⁰

Delaying reconstruction permits planned surgical reconstruction of the bladder and abdominal wall.²¹ This also permits the bladder template to grow to a greater size for reconstruction. Patients with very large public diastasis (>10 cm) can have staged osteotomy, with gradual reduction of the diastasis over 1–2 weeks, followed by abdominal and bladder closure.²² Reduction of recurrence of the diastasis can be facilitated by the use of an interpublic stainless bar.²³ Reconstruction of the abdominal wall is typically combined with reconstruction of the bladder. This may be done at the time of the fecal diversion, or alternatively, the bladder halves may be approximated to create a bladder exstrophy, which can be closed at a later date.²⁴

Complete reconstruction of the bladder with penile reconstruction, as described for classic bladder exstrophy, has also been successfully applied to the patient with cloacal exstrophy.²⁵ Although some patients have developed eventual voided continence, continence outcomes are dependent on the degree of neurological deficit, bladder size, pelvic floor support, and other factors.

The techniques of urinary reconstruction and clinical outcomes vary widely. The bladder is often inadequate for urinary storage. The hindgut has been used as an adjunct to increase bladder capacity as part of the urinary reservoir. The use of stomach was reported by Mitchell and colleagues in nine of 12 patients, with the benefit of preservation of the short intestine; Lund and Hendren preferred ileum when adequate lengths of intestine were available.^{17,26}

To achieve urinary dryness, further surgical reconstruction is almost always necessary in this patient group. Husmann and colleagues reported continence rate using a Young-Dees-Leadbetter bladder neck reconstruction at only 22% (a percentage that appeared unaffected by concomitant enterocys-toplasty). If patients were neurologically normal, continence rates improved to 40%, versus 7% with an associated myelomeningocele.²⁷ Urinary continence almost always depends on self-catheter-ization (i.e. clean intermittent catheterization [CIC]) in this population. Tightening of the bladder neck or complete bladder neck closure with construction of a nonorthotopic catheterizable channel (Mitrofanoff) is a reliable technique for urinary continence. Lund and Hendren reported that three of 40 reconstructed patients could void.¹⁷ Mitchell reported the use of an artificial urinary sphincter (AUS), with one patient who voids spontaneously with the AUS. However, for three other patients with an AUS, CIC had to be performed.²⁸ A follow-up series with a maximum of nine years had only one patient with primary continence. Two were able to void but still needed CIC to be performed.²⁹ Other patients with an AUS have suffered from erosion in other series. Endoscopic injected bulking agents have not produced continence in any patients in reported series.²⁷

6.7 Sexual Function and Fertility

Most male patients with cloacal exstrophy have significant separation of the two corporal halves and separation of the scrotum. The phallic components are also often unequal, with one on each side of the pelvis. The penis is also uniformly shortened and the components are always very small, but in 30% of patients, one of the halves is partly or totally absent.³⁰ Occasionally, it is present, but buried in the perineum, or located in the bladder plate.³¹

Early reports suggested that gender reassignment to female with immediate bilateral orchiectomy and eventual reconstruction was appropriate.³² Concerns have been raised that patients that had undergone reassignment to female early in life continued to have male-oriented psychosexual development.^{33,34} Although these findings have not been consistent across institutions,^{35,36} most institutions have moved to assigning gender that is consistent with the karyotype. Additionally, the availability of alternate methods of phallic reconstruction has also made gender-congruent assignment appropriate.^{37,38} Longer-term studies have reported that 46XY male patients who are raised and remain in a female gender identity struggle to form social relationships and have decreased sexual interest and activity, with any sexual attraction manifested is most often directed toward women. In contrast, 46XY male patients raised with a male gender identity have good social relationships with women and develop heterosexual interests.^{30,34}

Because of the small phallic size, commonly associated neurologic deficits, and complex anatomical reconstruction, sexual function is often compromised in the male population with cloacal exstrophy. The advent of phallic reconstruction has improved the sexual outcomes for male patients with cloacal exstrophy. This reconstruction however remains technically challenging. In a series from Toronto Sick Children's Hospital, all the male patients achieved a stretched length at, or just below, two standard deviations below the normal stretched phallic length. Serum testosterone levels were normal for post-pubertal boys. All the male patients in this series considered themselves sexually inadequate. Three of four patients received intensive psychiatric treatment.³⁸ The neurologic status of the lower spine impacts erectile function. As a consequence, those with a myelomeningocele typically have erectile dysfunction as noted in two of four adult patients.³⁸

Fertility is similarly adversely affected in this population, although the use of assisted reproductive techniques may make paternity possible. Reports in the literature do demonstrate that penetrative intercourse is possible for some men with cloacal exstrophy.^{34,38} Semen analysis has been reported for one man and was normal. In another it was attempted, but he had retrograde ejaculation.³⁸

The majority of female patients with cloacal exstrophy have concomitant genital anomalies. Naiditch *et al.* found that all 16 women in their series had a didelphic uterus; the presence of a single uterus has been reported.^{1,39} The two portions of the Müllerian system can be variable in size from half-normal to rudimentary. The ovaries and tubes are usually normal, but may have an abnormal insertion into the ureters laterally. The vaginal duplication is also common; some segments may be absent or rudimentary.³⁹

Only a small percentage of women with cloacal exstrophy are fertile and able to carry a pregnancy. Data from the reported literature suggests that 50% are sexually active, with reasons for abstinence including embarrassment about stomas, poor body image, and dyspareunia. At least three pregnancies have been reported, with two successful outcomes. In those women who have had successful reconstruction, pregnancy has been associated with uterine prolapse and cesarean section delivery is recommended.⁴⁰ However, as most have had previous urologic reconstruction, injury to the reconstructed bladder and continent stoma has been reported during cesarean section.

Pregnancy and delivery complications include rupture of a Kock pouch, uterine prolapse, and postpartum fecal and urinary incontinence.^{39,41}

6.8 Long-term Issues

Patients with cloacal exstrophy present with a wide range and severity of anomalies. As a consequence, assessment of successful outcomes remains challenging. The urologic anomalies of a bifid exstrophic bladder, and renal and genital abnormalities are impacted by the intestinal shortage that affects most of these patients as well. In 25% of patients, it is severe enough to cause life-threatening nutritional failure.^{1,42}

Concomitant conditions, such as the neural tube defect in 29% to 75% and skeleton and limb deformities in 12% to 65%, all contribute to the long-term aggregate morbidity of cloacal exstrophy.⁴² Outcomes vary; the outcome of reconstruction may be reasonable in one area and suboptimal in another, such that the overall quality of life may be difficult to determine for these patients. These patients likely do better when these anomalies are managed holistically; a team approach is valuable throughout the lifetime of these patients.

6.9 Key Recommendations

- Cloacal exstrophy is a complex multi-system congenital anomaly and it should be managed at a centre with subspecialty expertise in the care of critically ill infants whenever possible. (Grade of Recommendation [GOR] C)
- 2. Initial management should focus on medical stabilization and management of the spinal and gastrointestinal tracts. (GOR C)
- **3.** Gender assignment should be based on karyotype and not on adequacy of genital structures for reconstruction. (GOR C)
- Lifelong follow-up is required for preservation of renal function and nutritional support. (GOR C)

6.10 References

- 1. Hurwitz RS, Marzoni GA, Ransley PG, et al. Cloacal exstrophy: a report of 34 cases. J Urol. 1987;138(4 Pt 2):1060–1064.
- Lund DP, Hendren WH. Cloacal exstrophy: experience with 20 cases. J Pediatr Surg. 1993;28(10):1360–1368; discussion 1368–1369.
- 3. Austin PF, Homsy YL, Gearhart JP, et al. The prenatal diagnosis of cloacal exstrophy. J Urol. 1998;160(3 Pt 2):1179–1181.
- Della Monica M, Nazzaro A, Lonardo F, et al. Prenatal ultrasound diagnosis of cloacal exstrophy associated with myelocystocele complex by the 'elephant trunk-like' image and review of the literature. Prenat Diagn. 2005;25(5):394–397.
- 5. Calvo-Garcia MA, Kline-Fath BM, Rubio El, et al. Fetal MRI of cloacal exstrophy. Pediatr Radiol. 2013;43(5):593-604.
- Gobbi D, Fascetti Leon F, Tregnaghi A, et al. Early prenatal diagnosis of cloacal exstrophy with fetal magnetic resonance imaging. Fetal Diagn Ther. 2008;24(4):437–439.
- Jayachandran D, Bythell M, Platt MW, et al. Register based study of bladder exstrophy-epispadias complex: prevalence, associated anomalies, prenatal diagnosis and survival. J Urol. 2011;186(5):2056–2060.
- Gambhir L, Höller T, Müller M, et al. Epidemiological survey of 214 families with bladder exstrophy-epispadias complex. J Urol. 2008;179(4):1539–1543.
- Reefhuis J, Honein MA, Schieve LA, et al. Use of clomiphene citrate and birth defects, National Birth Defects Prevention Study, 1997-2005. Hum Reprod. 2011;26(2):451–457.
- 10. Reutter H, Boyadjiev SA, Gambhir L, *et al.* Phenotype severity in the bladder exstrophy-epispadias complex: analysis of genetic and nongenetic contributing factors in 441 families from North America and Europe. J Pediatr. 2011;159(5):825–831.e1.
- Mathews R, Jeffs RD, Reiner WG, et al. Cloacal exstrophy--improving the quality of life: the Johns Hopkins experience. J Urol. 1998;160(6 Pt 2):2452–2456.
- 12. Dutta HK. Cloacal exstrophy: A single center experience. J Pediatr Urol. 2014;10(2):329-335.
- Husmann DA, McLorie GA, Churchill BM, et al. Management of the hindgut in cloacal exstrophy: terminal ileostomy versus colostomy. J Pediatr Surg. 1988;23(12):1107–1113.
- Sawaya D, Goldstein S, Seetharamaiah R, et al. Gastrointestinal ramifications of the cloacal exstrophy complex: a 44-year experience. J Pediatr Surg. 2010;45(1):171–175; discussion 175–176.
- Levitt MA, Mak GZ, Falcone RA Jr, et al. Cloacal exstrophy--pull-through or permanent stoma? A review of 53 patients. J Pediatr Surg. 2008;43(1):164–168; discussion 168–170.
- Roth CC, Wilson BA, Kibar Y, et al. Application of a continent fecal reservoir in patients with cloacal exstrophy. J Urol. 2010;183(1):290–296.
- 17. Lund DP, Hendren WH. Cloacal exstrophy: a 25-year experience with 50 cases. J Pediatr Surg. 2001;36(1):68–75.
- Sawaya D, Gearhart JP. Gastrointestinal reconstruction and outcomes for patients with the OEIS complex. Semin Pediatr Surg. 2011;20(2):123–125.
- 19. Soffer SZ, Rosen NG, Hong AR, et al. Cloacal exstrophy: a unified management plan. J Pediatr Surg. 2000;35(6):932–937.
- Ben-Chaim J, Peppas DS, Sponseller PD, et al. Applications of osteotomy in the cloacal exstrophy patient. J Urol. 1995;154(2 Pt 2):865–867.
- Thomas JC, DeMarco RT, Pope JC 4th, et al. First stage approximation of the exstrophic bladder in patients with cloacal exstrophy--should this be the initial surgical approach in all patients? J Urol. 2007;178(4 Pt 2):1632–1635; discussion 1635–1636.
- Silver RI, Sponseller PD, Gearhart JP. Staged closure of the pelvis in cloacal exstrophy: first description of a new approach. J Urol. 1999;161(1):263–266.
- Mathews R, Gearhart JP, Bhatnagar R, et al. Staged pelvic closure of extreme pubic diastasis in the exstrophy-epispadias complex. J Urol. 2006;176(5):2196–2198.

- 24. Ricketts RR, Woodard JR, Zwiren GT, et al. Modern treatment of cloacal exstrophy. J Pediatr Surg. 1991;26(4):444–448; discussion 448–450.
- 25. Grady RW, Mitchell ME. Complete primary repair of exstrophy. J Urol. 1999;162(4):1415–1420.
- 26. Mitchell ME, Plaire C. Management of cloacal exstrophy. Adv Exp Med Biol. 2002;511:267–270; discussion 270–273.
- Husmann DA, Vandersteen DR, McLorie GA, et al. Urinary continence after staged bladder reconstruction for cloacal exstrophy: the effect of coexisting neurological abnormalities on urinary continence. J Urol. 1999;161(5):1598–1602.
- Mitchell ME, Brito CG, Rink RC. Cloacal exstrophy reconstruction for urinary continence. J Urol. 1990;144(2 Pt 2):554–558; discussion 562–563.
- 29. Lee RS, Grady R, Joyner B, *et al.* Can a complete primary repair approach be applied to cloacal exstrophy? J Urol. 2006;176(6 Pt 1):2643–2648.
- Meyer-Bahlburg HF. Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. Arch Sex Behav. 2005;34(4):423–438.
- 31. Shaw MB, West K, Gitlin J, et al. Intravesical phallus in cloacal exstrophy. Urology. 2003;61(3):644.
- 32. Tank ES, Lindenauer SM. Principles of management of exstrophy of the cloaca. Am J Surg. 1970;119(1):95–98.
- Reiner WG. Psychosexual development in genetic males assigned female: the cloacal exstrophy experience. Child Adolesc Psychiatr Clin N Am. 2004;13(3):657–674, ix.
- Reiner WG, Gearhart JP. Discordant sexual identity in some genetic males with cloacal exstrophy assigned to female sex at birth. N Engl J Med. 2004;350(4):333–341.
- Baker Towell DM, Towell AD. A preliminary investigation into quality of life, psychological distress and social competence in children with cloacal exstrophy. J Urol. 2003;169(5):1850–1853.
- 36. Schober JM, Carmichael PA, Hines M, et al. The ultimate challenge of cloacal exstrophy. J Urol. 2002;167(1):300-304.
- Massanyi EZ, Gupta A, Goel S, et al., Radial forearm free flap phalloplasty for penile inadequacy in patients with exstrophy. J Urol. 2013;190(4 Suppl):1577–1582.
- Husmann DA, McLorie GA, Churchill BM. Phallic reconstruction in cloacal exstrophy. J Urol. 1989;142(2 Pt 2):563–564; discussion 572.
- 39. Naiditch JA, Radhakrishnan J, Chin AC, *et al.* Fate of the uterus in 46XX cloacal exstrophy patients. J Pediatr Surg. 2013;48(10):2043–2046.
- Mathews RI, Gan M, Gearhart JP. Urogynaecological and obstetric issues in women with the exstrophy-epispadias complex. BJU Int. 2003;91(9):845–849.
- 41. Gezer A, Guralp O, Yesilbas C, *et al.* Spontaneous pregnancy and birth with corrected cloacal exstrophy. Acta Obstet Gynecol Scand. 2011;90(4):413–414.
- 42. McHoney M, Ransley PG, Duffy P, *et al.* Cloacal exstrophy: morbidity associated with abnormalities of the gastrointestinal tract and spine. J Pediatr Surg. 2004;39(8):1209–1213.



Cloacal and Urogenital Sinus Anomalies

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7.1 Introduction

Anorectal malformations (ARMs) represent a complex group of congenital anomalies resulting from abnormal development of the hindgut, allantois and Mullerian duct promoting complete or partial urorectal septal malformations. There is a wide variety of phenotypic expression, ranging from mild anorectal to very complex severe ARM. More than 75% of children with ARM have other associated malformations. Urogenital associations are one of the more common associations seen in ARM occurring in 20-45% of cases. In this chapter, we will revise cloacal and urogenital sinus abnormalities in order to provide updated knowledge and management as well as recommendations on specific clinical issues of this complex subject.

7.2 Embryology

The cloaca is an endoderm-lined primordial organ that is first apparent at the beginning of the second week of gestation.¹ This structure, which represents a confluence of the primitive hindgut (dorsally) and the allantois (ventrally) just before the fourth week of gestation, receives the mesonephric ductal system. The urorectal septum, which first appears during the fourth week of development, serves to separate the urogenital sinus (ventrally) from the anal canal (dorsally).² By weeks 6 to 7 of development, the urorectal septum has fused with the cloacal membrane and divided it into a ventral urogenital membrane and a dorsal anal membrane.³

The fibromuscular node of tissue that results from contact of the septum with the cloacal membrane serves as a critical insertion site for the perineal muscles and as the dividing point of the primitive cloacal sphincter complex into anterior (urogenital diaphragm) and posterior (external anal sphincter) components.

While the urorectal anlage is undergoing division, the developing mesonephric ducts, which have contacted the cloaca, enter the urogenital sinus near the müllerian tubercle.⁴ An offshoot of the mesonephric duct, the ureteric bud, extends cranially to induce development of the metanephric blastema. The terminal branch point of the ureteral bud from the mesonephric duct is later absorbed into the wall of the urogenital sinus. Proper incorporation of this complex results in the ureters opening at the lateral aspect of the trigone.

During cloacal development, paired müllerian ducts, which form from the coelomic epithelium, develop lateral to the mesonephric ducts and cross medially to fuse in the midline. The paired müllerian ducts then proceed caudally to join the urogenital sinus, where they produce an elevation called the müllerian tubercle. The caudal fusion of portions of these ducts normally leads to dissolution of the shared midline partition and the formation of a common uterovaginal canal, which as the name implies, gives rise to the uterus, cervix, and proximal two thirds of the vagina. Failure of septal regression can result in a number of possible müllerian duct abnormalities. **Figure 7-1**⁵ shows various abnormal presentations of urogenital and lower intestinal tract.





Several studies were conducted to define risk factors and interactions between gene susceptibility and environmental factors as a determinant role in the genesis of cloacal and urogenital abnormalities. The effect of drugs in pregnancy like thalidomide, retinoic acid has been appointed but epidemiological studies showed inconsistent results. Genetic implication has been suggested in pathogenesis of cloaca and UGS through failed angiogenesis influencing vascularization, development and differentiation of smooth muscle and nerves.

In a cloaca, the vagina, urethra and rectum are fused together; creating a common channel that opens into a single orifice at a topic urethral opening location (**Figure 7-1**). The length of this common channel can vary from short to long, ranging from 1 to 10 cm, frequently measuring 3-4 cm. A urogenital sinus, a terminal common channel for urinary and genital tract, which is a normal feature of the mature male fetus, represents a virilization of the female fetus, mostly due to congenital adrenal cortical hyperplasia. Both conditions have similar but also independent treatment strategies. Considering the reconstruction of the urinary tract in cloaca and UGS, the confluence location in relation to the bladder neck is a critical factor in surgical management.

7.3 Urogenital Sinus (UGS)

7.3.1 Classification

Classification of urogenital sinus has been historically divided in "high" (proximal/suprasphincteric) or "low" (distal/infrasphincteric)^{6,7,8} (LOE: 4), a concept used in cloaca that reflects ultimately the length of the common channel.

Other authors consider the location of the vagina in relation to the bladder neck as the most important information to plan the type of surgery (**Figure 7-2**).⁹ (LOE: 4). These authors propose a urogenital sinus classification that measures the exact distance of the common channel and the distance of the bladder neck to the vagina, as well as clitoral size and appearance of the external genitalia.⁹

FIGURE 7-2 A Rink proposed a classification by estimating endoscopically and measuring in centimeters the location of the vaginal confluence in relation to the bladder neck and the perineal meatus. The Vx,y description expresses the distance from vagina to bladder neck (x: white rows) and vagina to the urogenital sinus meatus (y: black arrows).

(Used with permission from: Rink RC, Adams MC, Misseri R, et al.9)



7.3.2 Clinical presentation and physical examination

As in other urological congenital disorders urogenital sinus abnormalities can be identified by antenatal ultrasonography. The finding of constant fluid-filled pelvic structures (vagina and bladder) like hydrometrocolpos in association with ambiguous genitalia is highly suspicious. Urinary hydrometrocolpos develops in patients with a urogenital sinus or cloacal anomaly,¹⁰ and various mechanisms have been attributed to the development of urinary hydrometrocolpos. These include stenosis at the junction of the vagina and the urogenital sinus, stenosis in the urogenital sinus resulting in distension of both bladder and vagina, and high position of the vaginal opening near the bladder base resulting in reflux of urine into the vagina.^{11,12}

Postnatal presentation of a virilized female fenotopic child and non-palpable gonads suggest congenital adrenal hyperplasia (CAH). A pediatric urologist should examine any patient with this clinical presentation at maternity or the patient should be referred as soon as possible. This is important for parental education about the disease and presenting a plan of treatment. Williams and Bloomberg have presented in 1976 a detailed clinical description of CAH and its different forms of presentation.¹¹ Congenital adrenal hyperplasia resulting from deficient 21-hydroxylase activity is an autosomal recessive disorder with an incidence of 1 in 5000 to 1 in 25 000 in Caucasian populations. A block in the conversion of 17-hydroxyprogesterone to 11-deoxycortisol in the zona fasciculata of the adrenal glands leads to reduced synthesis of cortisol and increased corticotropin production, which in turn promotes excess production and release of adrenal androgens. In the severe form the female fetus is virilized and in approximately 50 % of cases an associated defect in aldosterone synthesis may precipitate a life-threatening adrenal crisis in the early neonatal period. Hypertension can occur in children with genital ambiguity secondary to CAH with 11β-hydroxylase deficiency and tendency to dehydration may also lead to a diagnosis of CAH.

Physical examination is important to plan reconstruction (Figure 7-3). The size of the clitoris, the consistency of the erectile bodies, degree of curvature, presence or absence of palpable gonads, aspect of labioscrotal folds should be registered. The location of the anus should be documented, searching for anterior displacement that reminds embryological proximity to cloacal anomalies. A rectal examination is mandatory in these patients. The Prader classification expresses the amount of virilization of the patient, varying from 1 to 5 (Figure 7-4).¹³

FIGURE 7-3 Δ Different clinical presentation of patients with CAH and urogenital sinus. (Photos provided courtesy of Dr. Antonio Macedo.) C



FIGURE 7-4

The Prader classification allows reporting the amount of virilization

Used with permission from: White PC & Speiser PW. Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency. Endocrine Reviews 2000, 21 3: 245–291.13



7.3.3 Radiographic and endoscopic evaluation

The preoperative radiographic work-up is critical to provide the surgeon with detailed information concerning the length of the common urogenital sinus, the location of the vaginal confluence and its relation to the bladder neck. The size of the vagina, possibility of vaginal septum and presence of two vaginas, bladder and urethral anatomy should also be investigated.

Ultrasonography of the urinary tract and pelvis allows evaluation of kidneys, ovaries, and uterus and can find bladder or vaginal distention. Any enlargement of the adrenal glands suggests the possibility of CAH.¹⁴

A genitography consists of filling the bladder, urethra, vagina, and sinus with contrast. Sometimes it is possible to insert one catheter in the bladder and other in the vagina (**Figure 7-5**).

FIGURE 7-5

A genitography shows clearly the distance from vaginal confluence to the bladder neck and allows the surgeon a better planning of the procedure.

(Photo provided courtesy of Dr. Antonio Macedo.)



The confluence of the vagina in the urogenital sinus is sometimes sub-stenotic and may not fill with contrast. In this situation, magnetic resonance imaging (MRI) helps to define the anatomy in pure urogenital sinus anomalies or DSD conditions (**Figure 7-6**). It plays a role to indicate vaginal confluence to urogenital sinus although not so precisely as in endoscopy (**Figure 7-7**). There is a trend to perform endoscopy at the same time of reconstruction, so MRI can provide useful information when genitography fails to show the vagina.

FIGURE 7-6

MRI can be helpful when genitography does not allow vaginal confluence definition.

(Photos provided courtesy of Dr. Antonio Macedo.)





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FIGURE 7-7

Endoscopic view of urethra (above) and vagina (below) from the UGS.

(Photo provided courtesy of Dr. Antonio Macedo.)



7.3.4 Surgical reconstruction

7.3.4.1 **Gender assignment**

The first aspect of surgical reconstruction is to discuss with the parents the controversies of DSD regarding gender assignment. Indeed early adjustment of sexual genitalia contributes to psychosocial development.¹⁵ (LOE: 4).

Recently this statement has been questioned. On the other hand, raising a child with genital ambiguity can be even worse¹⁶ (LOE: 4). A detailed description of these issues is outside the context of this chapter.

7.3.4.2 **Timing and principles of surgery**

Surgery for UGS includes three steps:

- clitoroplasty;
- labioplasty; and
- vaginoplasty.

A combined treatment is recommended for most patients, although high vaginal confluence is treated by some authors only after puberty^{16, 17,18,19,20,21} (LOE: 3) due to higher rates of vaginal stenosis and as a way to avoid vaginal dilatation during early childhood.

The ideal timing for surgery is an ongoing debate. A consensus statement on CAH from the European Society for Pediatric Endocrinology recommends surgery in the 2- to 6-month-old range for those with a high vaginal confluence. Recently a clinical practice guideline published by the Endocrine Society for patients with CAH suggest "that severely virilized Prader stage \geq 3 females, clitoral and perineal reconstruction should be considered in infancy"²² (LOE: 4). Clitoroplasty should provide cosmesis but also spare clitoral innervation for future sexual sensibility. The neurovascular anatomy studies of the clitoris presented by Baskin and associates (1999) suggest that ventral incision preserve the dorsal neurovascular bundle and branches laterally.²³ Others preserve Buck's fascia with the neurovascular bundle and glans and afterwards the corporeal bodies are mobilized and disassembled. Each corporal body is placed in the ipsilateral labial fat, and theoretically this method allows reversal of the feminizing genitoplasty if it proves to be necessary²⁴ (LOE: 4).

Vaginoplasty techniques include commonly a posteriorly based perineal flap described by Fortunoff and coworkers in 1964²⁵ and modified as an omega-shape by others to improve cosmesis^{26,27} (LOE: 3). Flap vaginoplasty exclusively is not recommended for high vaginal confluence, since it may result in a short hypospadiac urethra, vaginal voiding and infections.^{28,29}

The pull-through vaginoplasty requires separation of the vagina separated from the urogenital sinus, which is used to create the urethra. The mobilized vagina may reach the perineum, but in most cases skin flaps are necessary.

Complete vaginal replacement is performed in severe cases.

Labioplasty techniques are performed by using the split phallic skin and this is moved caudally to create a normal cosmetic appearance of the external genitalia.

7.3.5 **Operative technique step-by-step**

All steps of surgery are illustrated on (**Figure 7-8** and **7-9**). A circumferential incision around the glans associated with two parallel longitudinal lines on either side of the ventral mucosal strip (urethral plate equivalent) extending around the meatus is performed. A perineal omega-shaped incision up to the meatus is performed, exposing the perineum and urogenital sinus. The phallus is degloved as in hypospadias repair up to the level of the bifurcation of the corporeal bodies and the pubis dorsally. The phallus is detached from the urogenital sinus and a tourniquet is placed at the base. A longitudinal incision is then made through Buck's fascia on the ventral aspect of each corporeal body, which is excised without further incisions and sparing the dorsal area where the bundles are situated. A proximal suture of corporal tissue is required.

Glans reduction and clitoroplasty is done with care and excision should be performed ventrally. The neoclitoris and its neurovascular pedicle can be later repositioned after vaginal repair. The urogenital sinus is incised dorsally in the midline up to the vaginal confluence. Stay sutures in the vagina are placed and it is dissected from the rectum (posteriorly) and from bladder and urethra (anteriorly) to promote vaginal advance (pull-through technique). Both planes of dissection are difficult, since there is no obvious plane of dissection, and great care must be taken to avoid injury to the urinary tract and its sphincteric mechanism.

Passerini-Glazel (1989) described the use of the mobilized sinus which is divided dorsally in two flaps that he initially tubularized with phallic skin and later used as a flap to form the anterior vaginal wall.^{30,31} Phallic skin can also be used to construct the vaginal vestibule and anterior wall.³²

The mobilized phallic skin can be divided longitudinally in the midline up to the base to allow a clitoral hood, whereas the split preputial skin is moved inferiorly and anastomosed to the lateral vaginal wall. A bladder neck operation (YV-plasty) adjusts the redundant skin to reconstruct the labia minora and majora up to the vaginal introitus.

7.3.5.1 **Total and partial urogenital mobilization**

In 1997, Alberto Pena described a procedure called "total urogenital mobilization" (TUM) in which the sinus is dissected circumferentially and mobilized towards the perineum.³³ An advantage of this technique is a reduction in complications rate and the possibility of using the mucosa of the sinus to create a mucosal vestibule as a Passerini-like flap. Essentially, the TUM procedure was developed for cloacal repairs and adapted to urogenital sinus surgery aiming to simplify the reconstructive procedure for creating a vagina by eliminating the challenging step of dividing the urethra from the vagina. Rink *et al* have suggested that if the sinus is split laterally and rotated posteriorly it could also replace posterior vaginal surface^{34,35} (LOE: 4). Rather than discard the mobilized sinus, it should be used to provide a mucosa-lined vestibule. This statement was confirmed by Gosalbez *et al*, who reported excellent results on 11 patients with urogenital sinus anomalies who had undergone a modified Fortunoff technique combining total urogenital mobilization with the creation of urogenital sinus flaps.³⁶

Some authors consider this procedure of risk for sphincteric musculature and nerve injury, that could possibly lead to stress incontinence or foreshortening of the vagina. A modification proposed by Rink and associates^{35,37} (LOE: 4) was named "partial urogenital mobilization" (PUM), where circumferential dissection stops at the level of the pubo-urethral ligament, avoiding aggressive retropubic and suprapubic dissection.

FIGURE 7-8

Initial presentation, lines of incision and aspect of phallus and urogenital sinus after phallic degloving.

(Photos provided courtesy of Dr. Antonio Macedo.)





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FIGURE 7-9

Total urogenital mobilization of UGS (A), corporal bodies are sectioned from the basis from 3 to 9 o-clock position with dorsal Buck's fascia preservation (including the neurovascular bundles) (B), the UGS is opened dorsally up to vaginal confluence and define two mucosal flaps used for anterior and lateral vaginal wall reconstruction (C), end aspect after Y-V phallic skin adjustment for minor and major labia reconstruction (D).

(Photos provided courtesy of Dr. Antonio Macedo.)



7.3.5.1.1 The high urogenital sinus

The length of the urethra instead of the length of the common channel is important to recognize the high UGS (urethral length is less than 1.5 cm). In these patients, there is controversy regarding morbidity of UGS mobilization in terms of risk for urinary incontinence by bringing the bladder neck too low. Some authors prefer the anterior sagittal transrectal approach (ASTRA)³⁸ and claim that it allows excellent exposure of the proximal urethra and bladder neck, ensuring safe dissection and optimal separation of the vagina from adjacent structures. These authors reported on a total of 23 children with a mean age of 2.3 years [range 3 months to 17 years] with a high urogenital sinus with¹⁶ or without⁷ congenital adrenal hyperplasia. Mean follow-up was 3.4 years [range 14 months to 7 years]. There were no postoperative urethrovaginal fistulas. All toilet-trained patients were continent for feces and most were voiding normally per urethra (LOE 3).²¹

This technique contrasts with Peña's posterior sagittal anorectal approach, with complete anterior and posterior transection of the anorectal sphincteric muscles, for the surgical treatment of high UGS and can be considered a simplification of it.

Gonzales and Ludwikowski contested this opinion by attesting that TUM can always be accomplished perineally with the patient in the dorsal lithotomy position, so they abandoned techniques that separate the urethra from the vagina and have not observed any alterations in voiding or continence.³⁹ They recognize however that it excludes cases of UGS not associated with virilization, by whom the urethra may be too short and the surgical correction needs to be individualized and then the ASTRA approach may be useful. More recently, laparoscopic mobilization, transection, and pull-through of the vagina with a singlestep procedure proved to result in excellent functional and cosmetic outcome in a rare case of suprasphincteric UGS, hydrometrocolpos, and normal external genitalia has been reported by Fuchs *et al.*⁴⁰ Exposure of the urethral–vaginal junction could be significantly improved, avoiding division of the rectum and protective colostomy. Extensive vaginal mobilization and direct perineal anastomosis could be performed without skin flap augmentation of the vaginal wall. The approach resulted in good cosmetic and unimpaired functional outcome. Voiding cystourethrography showed normal lower urinary tract anatomy. No disturbances of bladder function could be detected 2 years after surgery. This approach is innovative and may simplify complex reconstructive approach, but needs further evidence that good results can be reproduced.

7.3.6 **Results and conclusion**

Feminizing genitoplasty results should be evaluated not only in the short term, but should also include long-term outcomes with evaluation of cosmetic appearance, female satisfaction, intercourse, sexual satisfaction and orgasm. However few publications on functional results with long-term data are available.

Data from 1976 showed that 25 of 84 patients undergoing vaginoplasty required a secondary procedure to provide a vaginal outlet satisfactory for intercourse; 5 of these 25 also required a third procedure⁴¹ (LOE: 3). Results of attempted coitus in 42 women with CAH 23.6 years after vagina repair showed satisfactory coitus in 62%. This literature may be reflecting old-fashioned procedures like "cut-back" vaginoplasty, differently from TUM or PUM, the most accepted technique nowadays.

Revisions of vaginoplasty have better outcomes when performed near puberty. Vaginal stenosis varied in published series from 16%^{42,43} to 37%.^{43,44} On the other hand, there is data available suggesting less vaginal stenosis when surgery was performed in early single-stage repair [3.4%] than as late vaginoplasty [42.8%]⁴⁴ (LOE: 3).

Burgu *et al.* reviewed a large series of vaginoplasties from the Great Ormond Street Hospital aiming to analyze the long-term outcomes of vaginal reconstruction, comparing techniques and timing. The authors found 63 patients who underwent a total of 71 vaginoplasties from 1985 to 2000. The techniques used were posterior skin flap,⁴² intestinal replacement²¹ and pull through.⁸ The majority of operations were performed before puberty [63%] and as primary procedures [79%]. Presenting diagnoses were congenital adrenal hyperplasia,²³ cloacal exstrophy,⁸ true persistent cloaca,¹² androgen insensitivity,⁸ urogenital sinus anomaly,⁶ and others.⁶ Strictures and discharge were the most common problems. The authors concluded that when vaginoplasty is the only indicated operation, delaying until puberty may minimize complications. When other genital surgery is indicated pre-pubertal vaginoplasty should be performed, since the second procedure usually involves simple dilatations and is associated with good results⁴⁵ (LOE: 3).

In regards to the clitoris, Minto and coworkers (2003) found it to be cosmetically normal in 59%, excessive in 20%, large in 7%, small in 7%, and absent in $7\%^{46}$ (LOE: 3).

Sensitosensory data are not sufficient to interpret erotic sensitivity, so further studies should be designed to record potential for orgasm in these patients.

Long-term data for TUM and PUM is still lacking. Continence may be an issue in future evaluation, although early reports suggest no compromising^{29,47,48,49} (LOE: 3). Recently Palmer *et al.* reviewed retrospectively 25 patients who underwent total or partial urogenital mobilization with a focus on postoperative continence status. They included a total of 14 patients with CAH, 5 with urogenital sinus and 6 with a cloacal anomaly. The patients were managed by total¹⁸ or partial⁷ urogenital mobilization procedures with a mean follow-up of 4.41 years [range 0.21 to 12.1]. They found that 21 of 22 patients [95.5%] were continent by age 3 years and there were no urinary complications⁵⁰ (LOE: 3).

The same authors found in the literature 111 patients with CAH or urogenital sinus, with 107 in 7 studies being continent [96.4%] by age 3 to 4 years. In 4 studies 32 patients were identified with cloacal anomalies who underwent total or partial urogenital mobilization, of whom 28 [87.5%] were continent by age 3 to 4 years. They conclude that the urinary continence rate was 96% in the CAH/ urogenital sinus group and 89.5% in the cloacal group. Detailed information about groups can be seen in (**Table 7-1**; reproduced from Palmer's publications).

References	Diagnosis	Type of surgery, n	Median age at surgery, mo (range)	Median y at follow-up (range)	No continent/ total No (%)
Palmer <i>et al.</i> 2012	CAH/UGS	13 TUM, 6 PUM	15 (10-211) for TUM, 22 (6-149) for PUM	5.8 (0.2-11) for TUM, 4.7 (0.3-12) for PUM	11/12 (91.7) for TUM, 4/4 (100) for PUM
Camanni <i>et al.</i> 2009	САН	6 TUM	10 (8-34)	5 (5-6)	5/5 (100)
Leslie <i>et al.</i> 2009	САН	18 TUM, 26 PUM	13 (3-174) for TUM, 12 (4-149) for PUM	Not reported	18/18 (100) for TUM, 26/26 (100) for PUM
Savanelli <i>et al.</i> 2008	CAH	14 PUM	16 (6-48)	Not reported	14/14 (100)
Braga <i>et al.</i> 2006	САН	24 PUM	41.4 (1-192)	2.1 (Not reported)	18/20 (90)
Gosalbez <i>et al.</i> 2005*	CAH/UGS	9 TUM	3.8 (3-156)	2.5 (0.25-5)	9/9 (100)
Kryger and Gonzalez 2004	CAH/mixed gonadal dysgenesis/ Pure gonadal dysgenesis/ true hermaphrodite	13 TUM	Not reported (5-216)	3.4 (0.4-4.8)	11/13 (84,6)
Jenak <i>et al.</i> 2001	CAH/UGS/true hermaphrodite	6 TUM	Not reported (4,5-234)	Not reported (0.8-7.5)	6/6 (100)

TABLE 7-1 Continence after PUM and TUM

* Patients with CAH/UGS/cloacal anomalies were not separated and, therefore, reported median age at surgery and median follow-up are for total population. From: Palmer B, Trojan B, Griffin K *et al.* Total and Partial Urogenital Mobilization: Focus on Urinary Continence. J Urol 2012; 187: 1422-1426.⁵⁰ Finally, there is a trend that combined surgery, including vaginoplasty should be performed early on, although secondary introitoplasty may be necessary after puberty. Better results can be presumably obtained in high-volume tertiary centers.

7.3.7 **Recommendations**

- Urogenital sinus abnormalities diagnosed either by antenatal ultrasonography (presence of hydrometrocolpos) (Grade C) or by physical examination of a virilized female fenotopic child and non-palpable gonads suggest CAH demand more precise radiological investigation.
- Genitography and cystoscopy should be performed under anesthesia at operation site and an MRI preoperatively is highly suggested (Grade C).
- Early combined surgery at 6-12 months is recommended by most patients ideally through a perineal approach (Grade C).
- Urinary continence is high (Grade C) whereas late sexual function and clitoral sensitivity still require further investigation (Grade D).

7.4 **Cloaca**

7.4.1 Introduction

Common cloaca, also known as persistent cloaca, is a complex anorectal and genitourinary malformation in which the rectum, vagina and urinary tract are fused to form a single, common channel.¹ Common cloaca occurs exclusively in girls and comprises the most complex defect in the spectrum of anorectal malformations. The condition probably occurs in 1 in 20,000 live births.^{3,4} The length of this common channel is the deciding factor in the varied management of this condition. Surgical treatment is complicated and time-consuming, especially when the common channel is long.

Historically, repair of the rectal component alone was done initially, followed by secondary surgery for the urogenital sinus. Raffensperger and Ramenowsky first suggested a combined abdominoperineal, vaginal and rectal pull-through in 1973.⁵¹ Hendren published the most detailed reports on the subject of cloacal malformation repair. His reports emphasized an approach to repair the entire anomaly at the same time. He described the posterior sagittal approach, which was used to repair an imperforate anus and was first performed in 1982.⁵² Joint mobilization of the urogenital sinus after separation from the rectum reduced operating time significantly and provided excellent functional and cosmetic results.

7.4.2 **Diagnosis, clinical presentation and physical examination**

Similarly to urogenital sinus abnormalities, third-trimester fetal MRI can detect cloacal malformations with high position of the distal bowel and long common channel⁵³ (LOE: 3).

In this scenario, the rectum is focally dilated and does not extend below the bladder base. Although the rectal content can demonstrate a normal meconium signal, sometimes it will exhibit increased T2 signal (fluid) with or without bladder layering containing decreased T2 and increased T1 (meconium) signal. Abnormal signal in the colon or in the bladder is consistent with a recto-urinary fistula, which in a female fetus is characteristic of a cloacal malformation. Additionally third-trimester megacystis in a female fetus with decreased or normal amniotic fluid should raise concern for this malformation, and attention to the appearance of the colon should be paid to alternatively exclude megacystis-microcolon-intestinal hypoperistalsis syndrome. Eventually, low position of the distal bowel in the absence of hydrocolpos may not be detected.

The diagnosis of cloaca should be suspected in a female born with an imperforate anus and smallappearing genitalia. The diagnosis can be made clinically. Almost 90% of patients have associated urological problems. The goal of treatment of a female born with cloaca is to achieve bowel control, urinary control and sexual function, which include menstruation, intercourse and possibly pregnancy. Obstructive genital anomalies (imperforate hymen, vaginal atresia) or combined obstructive urogenital anomalies (persistent urogenital sinus, cloaca, blind hemivagina) can be responsible for visible fetal hydrocolpos. In cloacal anomalies, patients may present with abdominal distention due to hydrometrocolpos and/or bladder and intestinal distention. Hydrometrocolpos incidence can be so high as 63%^{54,55} (LOE: 3) (**Figure 7-10**).

Capito and coworkers reviewed the charts of 13 women referred for a third trimester pelvic MRI for cystic pelvic mass discovered in second trimester ultrasound.⁷² They evaluated MRI compared with postnatal surgical findings and concluded that MRI could exclude the diagnosis of cloacal malformation in nine cases with no false negative. Once a cloaca is ruled out, a different signal between the bladder and the hydrocolpos on T2 sequences is in favor of an isolated genital obstruction. In contrast, in case of urogenital sinus, the vagina is filled with a mixture of genital secretions and urine, which gives it an MRI signal similar to the bladder on T2 sequences.

Spinal cord abnormalities should be investigated and physical examination should search for sacral dimples, hair patch, or an area of abnormal pigmentation but especially an abnormal buttock crease or flattened buttocks as a result of sacral agenesis.



The aspect of the external genitalia varies from normal female presentation to ambiguous appearance, with a phallic structure. Cloacal anomalies can be associated with other organ systems abnormalities, such as renal anomalies (renal dysplasia and ureteropelvic junction obstruction). Sixty percent can have septation of the vagina and uterus,^{55,56} more than ten percent can have cardiovascular abnormalities, central nervous system problems and the vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities (VACTERL) association.

7.4.3 **Radiographic and endoscopic evaluation**

Antenatal diagnosis is suspected in cases of hydrocolpos in association with bladder distension and eventually ascites. Fetal MRI allows further investigation of anorectal anatomy.

Postnatal radiographic evaluation should be initiated by plain abdominal film⁵⁶ that can diagnose pelvic mass and calcifications due to meconium reflux. Ultrasonography allows investigation of pelvic organs (uterus) and lower and upper urinary tract. Other urinary abnormalities such as dysplasia, fusion anomalies, ectopia, ureteropelvic junction obstruction, and duplication have been seen in 33% to 83% of children with a persistent cloaca (LOE 3).^{57–59}

Genitography and endoscopy are essential for planning the operative procedure. The length of the urethra up to its communication with the cloaca should be recorded. The vaginal anatomy is complex and variable. Hendren reported on 154 patients, 66 had one vagina, 68 had two vaginas, and the vagina was absent in 20⁶⁰ (LOE: 3). Vaginal duplication is also a common feature; they can be of different size and one may enter laterally to the other. A cervix can be seen at the top of each vagina. Other uterine malformations such as bicornuate uterus, hypoplastic uterus, or uterus didelphus are frequently seen in one third of patients.

The rectal confluence usually occurs close to the vaginal confluence or even inside the vagina. The length of the common cloaca should be measured and its aspect resembles the urethra in half of cases and the vagina in the other half.

Magnetic resonance imaging is important for evaluating the lumbosacral spine, pelvic anatomy and musculature.

7.4.4 Surgical Reconstruction

7.4.4.1 **Timing and principles of surgery**

Initial management of a cloacal anomaly involves stabilization of the child, especially when presenting with abdominal distention or respiratory symptoms. Drainage and decompression of the bladder and vagina is conducted initially and a division colostomy should be performed. In case of recurrence of vaginal and vesical distension both can be managed by intermittent catheterization. Decompression of the gastrointestinal tract is done by colostomy. The site of colostomy is however controversial. There is a trend to move from a low-loop colostomy to a more proximal area like the right transverse colon or even the descending colon just after the colon takes off from its retroperitoneal attachment. A reason for it would be the possibility of using the colon for vaginoplasty and keeping the left colic blood supply spared for future pull-through. Similarly to urogenital sinus abnormalities, a combined repair of all structures is recommended. Hall and coworkers (1985) suggested in the past that vaginal surgery should be done after puberty, performing initially only a rectal pull-through.⁶¹ This required repeat rectal mobilization and more complex intestinal surgery and it should not be stimulated today. Definitive repair of a cloaca should be carried out between 6 to 12 months of age.

One has to be aware that longer common channels (> 3cm) have a higher incidence of other obstructive and refluxive urological abnormalities that have to be treated accordingly. (**Figure 7-11**) illustrates a patient with a cloaca with a common channel of 4 cm.



7.4.5 **Operative technique step-by-step**

A posterior sagittal anorecto-vaginourethroplasty (PSARVUP) is performed with the child in the prone position and the pelvis elevated on rolls. An electrical stimulator helps to determine the area of maximal contraction, which is identified, marked with a skin scribe and with stay sutures for later rectal placement. This maneuver allows identification of the external sphincter and muscle complex of the rectum and provides excellent exposure for separation of the rectum and vagina (or vaginas) from the cloaca.

The incision extends from the tip of the coccyx in the midline to the posterior aspect of the cloacal orifice (**Figure 7-12A**). Sutures are placed to mark the sphincteric muscular structures on either side as they are encountered. When a rectal fistula is identified, it is opened posteriorly and stay sutures are placed to help mobilizing the rectum away from the vagina (or vaginas) (**Figure 7-12B**). When the common channel is longer than 3 cm , the need of abdominal surgery is higher.

Subsequently, the vagina is separated from the urogenital sinus and a Fogarty catheter inserted in the UGS may help dissection. Stay sutures also help and avoid urethral injury (**Figure 7-13A–B**). Mobilization of the vagina may not be sufficient to reach the perineum and therefore a skin flap or even a bowel segment may be necessary to reconstruct the vagina (**Figure 7-13D**). When the vagina is extremely dilated, a lateral vaginal flap can be mobilized to reach the perineum.⁶² If a TUM is employed, the vagina and urethra are brought down together and vaginal separation may not be necessary or can be easier to perform.

The common cloacal channel should be closed in layers with absorbable sutures to create a urethra and a Foley catheter should be left indwelling for 10 -14 days (**Figures 7-12C** and **D**, **Figure 7-13C**). The vagina is then sutured to the perineum.

FIGURE 7-12

PSARVUP allows excellent approach to cloaca repair (A), rectal fistula identification (B), dorsal incision and measure of common channel (C), insertion of a Foley tube in the bladder (D).

(Photos provided courtesy of Dr. Antonio Macedo.)



FIGURE 7-13

Identification of vagina that is marked with stay sutures (A and B), closure of common channel to produce the urethra (C), ileal segment isolation for vaginoplasty (D).

(Photos provided courtesy of Dr. Antonio Macedo.)



Finally, the rectum is pulled through to the perineum, and placed in the marked area of the sphincteric muscle mass and anastomosed to the skin (**Figure 7-14**). Rectal dilation is begun gradually at 2 to 3 weeks after surgery (**Figure 7-15**). When the patient cannot void adequately and empty the bladder, clean intermittent catheterization (CIC) should be initiated.

FIGURE 7-14

Perineal pull-through of rectum and neovagina.

(Photos provided courtesy of Dr. Antonio Macedo.)



FIGURE 7-15

End aspect after surgery (A) and early postoperative presentation after 30 days (B), including rectal and vaginal dilatation (C).

(Photos provided courtesy of Dr. Antonio Macedo.)







7.4.6 **Results and conclusion**

When analyzing results of cloacal repair, several issues like urinary and fecal continence, sexual function including erotic sensitivity, quality of intercourse, presence of orgasm and fertility may be considered. Hendren's series of 141 patients, showed that 83 [59%] voided spontaneously, 40 [28%] required CIC, 4 [3%] had undergone urinary diversion, and 1 [0.7%] was continent with urinary diversion; only 5 [3.5%] were wet, and in 8 the results were too early to assess (63) (LOE: 3). Pena *et al.* (2004) reported on 193 patients evaluated for urinary continence and concluded that the length of the common channel correlated with spontaneous voiding. Overall continence with spontaneous voiding occurred in only half of the patients [54%], whereas the other 46% were dry with CIC [24% with a native urethra, 22% with a Mitrofanoff channel] (62). Interestingly, when the common channel was less than 3 cm, 28% required CIC; but if greater than 3 cm, 78% required CIC (LOE: 3).

Table 7-2 provides a summary of the literature^{36,50,64–68} focusing specifically on urinary continence after PUM and TUM repair.

Levitt and Peña described lessons learned from 490 patients (397 of whom underwent primary operations, and 93 who underwent reoperations after attempted repairs at other institutions) that comprise the main author's experience over more than 25 years. The authors divided their series into 2 distinct groups of patients where common channel measurement was known (n=400): group A were those with a common channel <3.0 cm (n=225, 56%) and group B had a common channel > 3 cm (n=175, 44%). The separation into these 2 groups has important therapeutic and prognostic implications, as the authors summarized in (**Table 7-3**).⁶⁹

TABLE 7-2 Urinary continence after TUM and PUM

References	Number and type of surgery	Median Mos Age at Surgery (range)	Median Yrs Follow-up (range)	No. continent/ Total No (%)
Palmer <i>et al.</i> 2012	5 TUM, 1 PUM	12 (5.7–75) for TUM, 13 for PUM	2.9 (0.2–6.6) for TUM, 1 for PUM	5/5 (100) for TUM, 1/1 (100) for PUM
Lahoti <i>et al.</i> 2010	25 TUM	18 (10-36)	Not recorded	24/25 (96)
Matsui <i>et al.</i> 2009	11 TUM	14 (5-30)	5 (3-6)	6/7 (85.7)
Camanni <i>et al.</i> 2009	6 TUM	6.5 (5-12)	8.5 (4-11)	6/6 (100)
Leclair <i>et al.</i> 2007	22 TUM	9.3 (1.6-28)	4 (1-13.5)	15/17 (88.2)
Gosalbez <i>et al.</i> 2005*	2 TUM	3.8 (3-156)	2.5 (0.25-5)	1/2 (50)
Shimada <i>et al.</i> 2005	4 TUM	21 (13-19)	3.7 (3-5)	4/4 (100)

* Patients with CAH/UGS/cloacal anomalies were not separated and, therefore, reported median age at surgery and median followup are for total population.

Updated: Palmer B, Trojan B, Griffin K *et al.* Total and Partial Urogenital Mobilization: Focus on Urinary Continence. J Urol 2012; 187: 1422-1426. (50, 64, 65, 66, 67, 36, 68)

TABLE 7-3 Prognostic implications after cloacal repair in regards to common channel length.

	Group A	Group B
Common channel	Short (<3 cm)	Long (>3 cm)
Type of operation	Only posterior sagittal	Posterior sagittal and laparotomy
Length of procedure	3 hours	6-12 hours
Postoperative hospitalization	48 hours	Several days
Incidence in our series	56% (n: 225)	44% (n: 175)
Voluntary bowel movements	66%	36%
Urinary continence	74%	28%
Intra-operative decision-making	Relatively easy, reproducible operation	Complex, delicate and technically demanding*

*Bladder/vagina separation, ureteral catheterization, vesicostomy, bladder neck reconstruction or closure, vaginal switch, vaginal replacement (with rectum, colon or small bowel).

Reproduced with permission from: Levitt MA, Peña A. Cloacal malformations: lessons learned from 490 cases. Semin Pediatr Surg 2010; 19: 128-138.⁶⁹

Levitt *et al.* reported 95 cloacal reoperations in patients that were repaired elsewhere. Indications for surgery were: persistent urogenital sinus,⁴⁶ rectal stricture or acquired atresia,⁴⁵ acquired vaginal atresia or stricture,⁴⁵ mislocated rectum,³⁶ urethrovaginal fistula,¹⁶ rectal prolapse,¹² urethral atresia or stricture,⁷ and rectovaginal fistula.⁵ In cases of persistent urogenital sinus, the surgeons were unaware of the presence of a cloaca, referring instead to the malformation as a "rectovaginal fistula." The authors observed that complications were most likely related to tension or ischemia or not simply diagnosing a cloaca and repairing the entire malformation and not just the rectum during the initial repair⁷⁰ (LOE 3).

An important aspect regarding bladder function after TUM has been addressed by Matsui *et al.* who retrospectively reviewed the records of 11 patients [median age 14 months] who underwent reconstruction of the cloaca by TUM. Urinary continence was assessed in 7 patients older than 4 years who underwent urodynamic studies. All patients exhibited detrusor underactivity or non-contractile detrusor, and 86% displayed normal bladder compliance after TUM (65) (LOE: 3). Interestingly Warne *et al* reported that a hypo- or non-contractile bladder was not due to the natural history, but was caused by TUM. One reason for this conclusion is that bladder dysfunction may be induced by a transabdominal approach for extensive mobilization of the rectum⁵⁵ (LOE: 3). In summary we have to consider that although the majority of cloaca patients will be continent after TUM, CIC and other reconstructive urinary procedures may be required in more than half of them. This is especially true in those patients presenting with sacral anomalies.

Fecal continence is directly related to the neurologic status^{71,68} (LOE: 3). Pena *et al.*(2004) reported that 60% of 156 patients had voluntary bowel movements but only 28% of them never soiled⁶² (LOE: 3). The Malone antegrade continence enema (MACE) appendicovesicostomy likewise used in myelomeningocele patients is extremely efficient to treat and prevent constipation and achieving fecal continence by refractory patients.

Renal insufficiency can be so high as 50% but may vary between 20% and 30%. Bladder function and dynamics should be followed but nowadays CIC prevents most of the complications that are common in patients with a neuropathic bladder.

7.4.7 **Recommendations**

- Cloacal abnormalities can be suspected prenatally in the presence of hydrometrocolpos on ultrasonography. The initial approach should involve stabilization of the child, drainage of the bladder and vagina and a proximal left colostomy (Grade A).
- Only high-volume tertiary centers should treat this complex disease (Grade A). A combined repair of all structures is recommended and carried out between 6 to 12 months of age (Grade C).
- The common channel plays a major role in clinical outcome. Longer common channels (>3 cm) have a higher incidence of other obstructive and refluxive urological abnormalities (Grade B). Urinary continence can be achieved only in 28% of those patients in contrast to 74% when the common channel is <3 cm (Grade C).</p>
- Vaginal stricture and fistula are common complications and should be recognized and treated early.
- Total fecal continence is seen in the minority of patients after surgery, so that MACE should be considered (Grade D).

7.5 **References**

- Grosfeld J. Anorectal anomalies. In: Zuidema GD, Condon RE (ED). Shackelford's surgery of the alimentary tract. Philadelphia, WB Saunders, 1996, p. 450.
- 2. Moore K, Persaud T. The developing human. Philadelphia, WB Saunders, 1995. p. 199–200.
- 3. Park JM. Normal Development of the Genitourinary Tract. In: Wein, AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA (ED). Campbell-Walsh Urology. Philadelphia, Elsevier Saunders, 2012, p. 2986.
- 4. Churchill B, Hardy B, Stephens CA. Urologic aspects of malformations and common abnormalities of the anus and rectum. Urol Clin North Am 1978; 5:141-154.
- Park JM. Normal Development of the Genitourinary Tract. In: Wein, AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA (ED). Campbell-Walsh Urology. Philadelphia, Elsevier Saunders, 2012, p. 2987.
- 6. Hendren WH, Crawford J. Adrenogenital syndrome: the anatomy of the anomaly and its repair. J Pediatr Surg 1969; 4:49-58.
- Powell DM, Newman KD, Randolph J. A proposed classification of vaginal anomalies and their surgical correction. J Pediatr Surg 1995; 30:271-275.
- 8. Rink RC, Kaefer M. Surgical management of intersexuality, cloacal malformation and other abnormalities of the genitalia in girls. In: Walsh P, Retik AB, Vaugh EP, Wein AJ (ED). Campbell's urology. Philadelphia, WB Saunders, 2002, pp 2428-2467.
- 9. Rink RC, Adams MC, Misseri R. A new classification for genital ambiguity and urogenital sinus anomalies. BJU Int 2005; 95:638-642.
- 10. Subramanian S, Sharma R, Gamanagatti S, *et al.* Antenatal MR diagnosis of urinary hydrometrocolpos due to urogenital sinus. Pediatr Radiol. 2006; 36(10):1086-9.
- 11. Williams DI, Bloomberg S. Urogenital sinus in the female child. J Pediatr Surg, 1976; 11:51–56.
- 12. Marshall FF, Jeffs RD, Sarafayan WK. Urogenital abnormalities in the female patient. J Urol, 1979; 122:568–572.
- White PC, Speiser PW. Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency. Endocrine Reviews 2000; 21(3): 245-291.
- Brock JI, Hernanz-Schulman M, Russel W, et al. Diagnosis of congenital adrenal hyperplasia by ultrasound in the newborn. Paper presented at a meeting of the American Academy of Pediatrics, Urology Section, San Francisco, 1998.
- Schober JM. Feminizing genitoplasty for intersex. In: Mouriquand PDE (ED). Pediatric surgery and urology: long term outcomes. London, WB Saunders, 1998, pp 549-558.
- 16. Rangecroft L. Surgical management of ambiguous genitalia. Arch Dis Child 2002; 88:799-801.
- Sotiropoulos A, Morishima A, Homsy Y, et al. Long-term assessment of genital reconstruction in female pseudohermaphrodites. J Urol 1976; 115:599-601.
- 18. Snyder III H, Retik AB, Bauer SB, et al. Feminizing genitoplasty: a synthesis. J Urol 1983; 133:1024-1026.
- Alizai N, Thomas D, Lilford RJ, et al. Feminizing genitoplasty for congenital adrenal hyperplasia: what happens at puberty? J Urol 1999; 161:1588-1591.
- Creighton S, Minto C, Steele SJ. Objective cosmetic and anatomical outcomes of adolescence of feminizing surgery for ambiguous genitalia done in childhood. Lancet 2001; 338:124-125.
- 21. Thomas D. Gender assignment background and current controversies. BJU Int 2004; 93(Suppl. 3):47-50.
- 22. Speiser P, White P. Congenital adrenal hyperplasia. N Engl J Med 2003; 349:776-788.
- 23. Baskin L, Erol A, Li YW, et al. Anatomical studies of the human clitoris. J Urol 1999; 162:1015-1020.
- Pippi Salle JL, Braga LP, Macedo N, et al. Corporeal sparing dismembered clitoroplasty: an alternative technique for feminizing genitoplasty. J Urol 2007; 178(4 Pt 2):1796-1800.

- Fortunoff S, Lattimer J, Edson M. Vaginoplasty technique for female pseudohermaphrodites. Surg Gynecol Obstet 1964; 118:545-548.
- 26. Jenak R, Ludwikowski B, Gonzalez R. Total urogenital sinus mobilization: a modified perineal approach for feminizing genitoplasty and urogenital sinus repair. J Urol 2001; 165:2347-2349.
- 27. Freitas-Filho L, Carnevale J, Melo CE, *et al.* A posterior-based omega-shaped flap vaginoplasty in girls with congenital adrenal hyperplasia caused by 21-hydroxylase deficiency. BJU Int 2003; 91:263-264.
- Hendren WH, Atala A. Repair of the high vagina in girls with severely masculinzed anatomy from the adrenogenital syndrome. J Pediatr Surg 1995; 30:91-94.
- 29. Rink RC, Adams MC. Evaluation and surgical management of the child with intersex. Prog Paediatr Urol 1999; 2:67-88.
- Passerini-Glazel G. A new 1-stage procedure for clitorovaginoplasty in severely masculinized female pseudohermaphrodites. J Urol 1989; 142:565-568.
- Passerini-Glazel G: Vaginoplasty and clitoroplasty for the adrenogenital syndrome. In: Hinman Jr F (ED). Atlas of pediatric urologic surgery. Philadelphia, WB Saunders, 1994, p. 635.
- 32. Gonzalez R, Fernandes E. Single stage feminization genitoplasty. J Urol 1990; 143:776-778.
- 33. Pena A. Total urogenital mobilization: an easier way to repair cloacas. J Pediatr Surg 1997; 32:267-268.
- 34. Rink RC, Cain MP. Further uses of the mobilized sinus in total urogenital mobilization procedures. Paper presented at annual meeting of the American Academy of Pediatrics, 2002, Boston.
- 35. Rink RC, Metcalfe PD, Cain MP, et al. Use of the mobilized sinus with total urogenital mobilization. J Urology 2006; 176(5):2205-2211.
- Gosalbez R, Castellan M, Ibrahim E et al. New concepts in feminizing genitoplasty—is the Fortunoff flap obsolete? J Urol 2005; 174: 2350.
- Rink RC, Metcalfe PD, Cain MP, et al. Partial urogenital mobilization: the advantages without the risks. Paper presented at annual meeting of the European Society of Pediatric Urology and also the American Academy of Pediatrics. Uppsala (Sweden); 2005.
- Pippi Salle JL, Lorenzo AJ, Jesus LE, et al. Surgical Treatment of High Urogenital Sinuses Using the Anterior Sagittal Transrectal Approach: A Useful Strategy to Optimize Exposure and Outcomes. J Urology 2012; 187: 1024-1031.
- 39. Gozalez R, Ludwikowski B. Management of the high urogenital sinus--risk of overexposure? J Urol 2012, 187: 787-788.
- Fuchs J, Warmann SW, Seitz G et al. Laparoscopically Assisted Vaginal Pull-through for High Urogenital Sinus: A New Surgical Technique. Urology 2012; 79 (5): 1180- 1183.
- Jones Jr HW, Garcia SC, Klingensmith GJ. Secondary surgical treatment of the masculinzed external genitalia of patients with virilizing adrenal hyperplasia. Am J Obstet Gynecol 1976; 48:73-75.
- 42. Al-Bassam A, Gado A. Feminizing genital reconstruction: experience with 52 cases of ambiguous genitalia. Eur J Pediatr Surg 2004; 14(3):172-178.
- Nordenskjold A, Holmdahl G, Frisen L, et al. Type of mutation and surgical procedure affect long-term quality of life for women with congenital adrenal hyperplasia. J Clin Endocrinol Metab 2008; 93(2):380-386.
- 44. Eroglu E, Tekant G, Gundogdu G, et al. Feminizing surgical management of intersex patients. Pediatr Surg Int 2004; 20:543-547.
- Burgu B, Duffy PG, Cuckow P et al. Long-term outcome of vaginal reconstruction: Comparing techniques and timing. J Pediatr Urol 2007; 3: 316-320.
- 46. Minto CL, Liaco LM, Woodhouse CR, et al. The effect of clitoral surgery on sexual outcome in individuals who have intersex conditions with ambiguous genitalia: a cross-sectional study. Lancet 2003; 361:1252-1257.
- Hamza AF, Soliman HA, Abdel Hay SA, et al. Total urogenital sinus mobilization in repair of cloacal anomalies and congenital adrenal hyperplasia. J Pediatr Surg 2001; 36:1656-1658.
- 48. Kryger JV, Gonzales R. Urinary continence is well preserved after total urogenital mobilization. J Urol 2004; 172:2384-2386.
- Rink RC, Leslie JA, Kaefer M, et al. Outcomes and risk factors in urogenital mobilization. Presented at the American Academy of Pediatrics, San Francisco, CA, October 26-29, 2007.

- 50. Palmer B, Trojan B, Griffin K *et al.* Total and Partial Urogenital Mobilization: Focus on Urinary Continence. J Urol 2012; 187: 1422-1426.
- 51. Raffensperger JG, Ramenofsky ML. The management of a cloaca. J Pediatr Surg. 1973; 8(5):647-57.
- 52. Hendren WH: Further experience in reconstructive surgery for cloacal anomalies. J Pediatr Surg 1982; 17:695-717.
- 53. Calvo-Garcia MA, Kline-Fath BM, Levitt MA *et al.* Fetal MRI clues to diagnose cloacal malformations. Pediatr Radiol 2011; 41:1117–1128.
- 54. Bartholomew T, Gonzales EJ. Urologic management in cloacal dysgenesis. Urology 1978; 11:549-557.
- 55. Warne S, Wilcox D, Creighton S, et al. Long-term gynecologic outcome of patients with persistent cloaca. J Urol 2003; 170:1493-1496.
- Jaramillo D, Lebowitz R. The cloacal malformation: radiologic findings and imaging recommendations. Radiology 1990; 177:441-448.
- 57. Kay R, Tank ES. Principles of management of the persistent cloaca in the female newborn. J Urol 1977; 117:102-104.
- 58. Warne S, Wilcox D, Ledermann SE, et al. Renal outcome in patients with cloaca. J Urol 2002; 167:2548-2551.
- Rink RC, Herndon CD, Cain MP, et al. Upper and lower urinary tract outcomes after surgical repair of cloacal malformation: a three-decade experience. BJU Int 2005; 96:131-134.
- 60. Hendren WH. Cloacal, the most severe degree of imperforate anus: experience with 195 cases. Am Surg 1998; 228:331-346.
- 61. Hall R, Fleming S, Gysler M, et al. The genital tract in female children with imperforate anus. Surg Gynecol Obstet 1985; 151:169-171.
- Pena A, Levitt MA, Hong A, et al. Surgical management of cloacal malformations: a review of 339 patients. J Pediatr Surg 2004; 39:470-479.
- De Filippo R, Shaul D, Harrison EA, et al. Neurogenic bladder in infants born with anorectal malformations; comparison with spinal and urologic status. J Pediatr Surg 1999; 34:825-827.
- Lahoti BK, Aggarwal G, Satsangi RK et al. Total urogenital sinus mobilization in common cloaca: Expirience of 25 cases. J Pediatr Urol. 2011;7(2):219-23.
- Matsui F, Shimada K, Matsumoto F et al. Bladder Function After Total Urogenital Mobilization for Persistent Cloaca. J Urol 2009; 182: 2455-2459.
- Camanni D, Zaccara A, Capitanucci ML et al. Bladder after total urogenital mobilization for congenital adrenal hyperplasia and cloaca— does it behave the same? J Urol, suppl. 2009182:1892.
- Leclair MD, Gundetti M, Kiely EM *et al.* The surgical outcome of total urogenital mobilization for cloacal repair. J Urol 2007; 177: 1492.
- Shimada K, Matsumoto F, Tohda A, et al. Urinary control after the definitive reconstruction of cloacal anomalie. Int J Urol. 2005;12(7):631-6.
- 69. Levitt MA, Peña A. Cloacal malformations: lessons learned from 490 cases. Semin Pediatr Surg 2010; 19: 128-138.
- Levitt MA, Bischoff A, Peña A. Pitfalls and challenges of cloaca repair: how to reduce the need for reoperations. J Pediatr Surg 2011; 46: 1250–1255.
- Peña A. The surgical management of persistent cloaca: results in 54 patients treated with a posterior sagittal approach. J Pediatr Surg 1989; 24:590-598.
- Capito C, Belarbi N, Jaouen AP, et al. Prenatal pelvic MRI: Additional clues for assessment of urogenital obstructive anomalies. J Ped Urol 2014; 10: 162-166.





Pediatric Varicocele, Micropenis, Buried and Webbed Penis, Penile Torsion, Diphallia, Penoscrotal Transposition, and Aphallia

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8.1 Pediatric Varicoceles

8.1.1 Introduction

A varicocele is an abnormal dilatation of the pampiniform plexus of veins. Varicoceles are associated with testicular pain, changes in testicular size, and decreased fertility potential. The decision to intervene in pediatric varicocele (PV) is based on several parameters and diagnostic tests. Management of varicoceles may range from watchful waiting or observation to open surgery. All of the different techniques have their own attendant risks, benefits, and complications.

As in adults, varicoceles are found in 8% to 16% of the pediatric population¹ (LOE 1). The management of varicoceles involves the initial use of ultrasound to measure size, testicular volume, and blood flow. Serial follow-ups may be done to determine any detrimental change in testicular size and symptomatology. The decision for intervention is then determined by the surgeon.

The management of PV differs in a key aspect from adult varicoceles in that semen parameters are most often unavailable. Also, the ultimate endpoint, which is paternity, is not observed in this age group. However, theoretical parameters such as testicular volume, size, blood flow in the testicle, and associated vascular supply can determine the need for intervention.

8.1.1.1 **Methods**

A systematic literature search was performed in PubMed for the past 10 years with the following key words: pediatric varicocele, varicocele children, varicocele adolescent with the following limitations, clinical trials, meta-analyses, review, randomized clinical trials, and comparative study.

A total of 1151 publications were found and screened by title and abstract. Of these, 174 publications were included in this review. The studies were then assessed according to the different levels of evidence and grades of recommendation following the International Consultation on Urological Diseases (ICUD) Grades of Recommendation (GOR) and Levels of Evidence (LOE). Unless indicated otherwise, all cited papers had an LOE of 3.

The following topics will be discussed in this chapter:

- Epidemiology and demographics
- Diagnostic modalities
- Indications for surgery

- Management strategies, including operative management
- Post-operative consequence and paternity
- Prevention of PV

8.1.2 **Epidemiology and Demographics**

8.1.2.1 Incidence

Varicocele incidence has been investigated in several studies and has been found to range from 10.13% to 18% in children and 42.7% in adolescents.^{2,3} Left-sided varicoceles are usually high grade and palpable, and right sided varicoceles are usually subtle.⁴ In one series, the left testes were also noted to be atrophic in 71% of the children and adolescents with varicocele.⁵ In another study, varicocele

prevalence was highest in the 15–19 years age group (14.1%) compared to younger age groups.⁶ The varicocele was found to be unilateral in 89.7% of the boys participating in the study. Prevalence of varicoceles and testicular atrophy were noted to increase with age (LOE 2). This increase in prevalence (15.8%) in boys aged 15 was confirmed elsewhere.⁷ Studies examining race found the same incidence of varicocele among black and white adolescents.⁸ A progression of subclinical varicocele prevalence (16.8%) to clinically detectable varicocele (28%) over a 4-year period has been noted.⁹

8.1.2.2 Sperm abnormalities

Sperm abnormality studies in unoperated adolescents have shown that patients with testicular asymmetry showed significantly lower median sperm concentrations and quality and were more likely to have abnormal spermiograms (based on the World Health Organization adult criteria)¹⁰ (LOE 2). Teenagers undergoing varicocelectomy also had pathologic changes on testicular biopsy.¹¹

8.1.2.3 **Vascular abnormalities**

Vascular anatomy has been studied using trans-scrotal antegrade venotesticulography, and three patterns have been identified:

- 1. Drainage to left testicular vein
- 2. Drainage to left cremasteric vein
- 3. Simultaneous drainage to both testicular and cremasteric veins

Incompetence of the left testicular vein and impaired drainage of the left external iliac veins with development of retrograde flow at the left cremasteric vein are the most frequent causes of varicocele in children.¹² The saphenofemoral junction has also been noted to be incompetent in patients with varicocele.¹³ The testicular veins of boys following varicocelectomy showed several morphological changes, including large lumen, sclerosis, and well developed muscularis.¹⁴

8.1.2.4 Laterality

Contact thermography and venography have shown significant retrograde flow in spermatic veins.¹⁵ It should be noted that, in this study, physical examination missed 7.2% of the left varicoceles and 87.5% of varicoceles on the right side. It has also been noted that the left testes are smaller than the right testes in boys for all stages, and the right testes in boys with varicoceles were smaller than in normal boys.¹⁶

8.1.2.5 **Tanner stage**

Tanner stage was studied in relation to varicoceles, and it was found that patients with Tanner 1–3 had a significantly higher incidence of testicular asymmetry (58–67%) compared to Tanner 4–5 (35%–39% asymmetry).¹⁷

8.1.2.6 **Somatometric parameters**

Height, weight, Tanner characteristics, and penis dimensions have been studied in relation to varicoceles. Stavropoulos *et al.* showed that boys with varicocele had significantly lower weight than boys without varicocele.¹⁸ Height was not significantly different between the two groups. Baek *et al.* prospectively studied testicular volume, height, weight, age, testicular volume, body mass index (BMI), and the presence and severity of varicoceles.¹⁹ They found that left varicoceles were significantly more common than right varicoceles. Testicular size discrepancy increased with severity of varicocele, and BMI had a significantly inverse relationship with varicoceles occurrence. Increased height and weight have been found to be associated with increased incidence of varicoceles.^{20,21} Increased varicoceles are correlated with penile length and inversely correlated with left testicular volume, BMI, and pubic hair. Varicoceles are more prevalent in older, taller boys with lower BMIs.^{22,23} (LOE 2).

8.1.2.7 **Sports and varicocele**

Two studies looked at sports and athletics in relation to the incidence of varicoceles. Zampieri and Dall'Agnola investigated healthy athletes and non-athletes compared to athletes with subclinical varicoceles and found that progression from subclinical to clinical varicoceles was significantly greater in the latter group.²⁴ Athletes who trained longer also had a higher incidence of varicoceles.²⁵

8.1.2.8 Siblings

Varicocele incidence in brothers of index patients were studied and compared to controls.²⁶ Of the index patients, 69.6% had grade III varicoceles and 26.7% of the brothers had grade III varicoceles. Brothers of patients had a 4.5-fold significantly greater incidence of varicoceles than controls. This suggests that first-degree male relatives of index patients should be evaluated.

8.1.3 **Diagnostic modalities**

Varicocele is mostly asymptomatic in the pediatric age group. A routine visit to a pediatrician may uncover it, or it may be noticed by either the patient or the patient's parents. The diagnosis of varicocele depends on a clinical finding of a collection of dilated and tortuous veins in the upright posture that is more pronounced when performing the Valsalva manoeuvre (**Figure 8-1**). Varicocele that are only palpable during the Valsalva manoeuvre are classified as grade I. Those which are palpable without the need for the Valsalva manoeuvre are classified as grade II. Varicocele that are visible at a distance even without palpating are classified as grade III. If venous reflux in the pampiniform plexus is seen only using scrotal Doppler ultrasound, the varicocele is classified as subclinical.



Varicocele—ultrasound with valsalva maneuvre

(Photo provided courtesy of Dr. H. Teo, KK Women's and Children's Hospital, Singapore, with permission.)



Doppler ultrasound examination of the scrotum assesses the testicular volume to discriminate testicular hypoplasia and can be used to determine growth arrest in pediatric varicoceles.²⁷ It is an excellent, safe, and highly sensitive pre-operative diagnostic tool, thereby validating its routine use for evaluating patients with scrotal diseases.²⁸ The use of colour Doppler ultrasonography (CDUS) influences surgical techniques in pediatric varicocele (**Figure 8-2**). Pre-operative CDUS measurements of maximal reflux velocity and total cross-sectional area can predict the number of internal spermatic

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veins requiring ligation, which is related to significant improvement of semen parameters after varicocelectomy.²⁹ Colour Doppler ultrasonography has also been used to determine the type of surgical approach (laparoscopic versus open microsugical subinguinal approach) according to Coolsaet type. In one study, CDUS was used to distinguish between Coolsaet type 1 and Coolsaet type 3 varicocele.³⁰ Patients with Coolsaet type 1 varicocele underwent laparoscopy while patients with Coolsaet type 3 varicocele (with iliac deferential reflux) underwent open surgery. No recurrences were noted in either group, suggesting that CDUS is a reliable diagnostic tool that can distinguish varicocele that can be treated laparoscopically from varicocele that should be treated with open surgery (LOE 2).

FIGURE 8-2

Varicocele—ultrasound with colour Doppler study

(Photo provided courtesy of Dr. H. Teo, KK Women's and Children's Hospital, Singapore.)



The orchidometer is a calliper used to measure testicular volume. Compared to scrotal Doppler ultrasound, the orchidometer is more feasible and has a cost-benefit advantage.³¹ However, scrotal Doppler ultrasonography is superior in diagnosing testicular growth arrest among pediatric varico-cele patients³² (LOE 2). Clinical varicoceles can be predicted with high accuracy based only on the diameter of testicular veins using cut-point values at rest and during the Valsalva manoeuvre.³³

Scrotal thermography is a diagnostic method that measures temperature differences across the skin surface using a highly sensitive infrared camera. It is a feasible, short, and low-cost diagnostic method for varicocele. However, further studies on a larger number of patients are needed to evaluate the sensitivity and specificity of this method.³⁴

8.1.4 Indications for surgery

Varicoceles are a major cause of male factor infertility. Surgical indications for correcting pediatric varicocele include high-grade varicocele, pain, and testicular hypotrophy/growth arrest. Statistically significant relationships have been found between testicular growth arrest and high varicocele grade, and between grade of reflux and testicular growth arrest, as determined by scrotal Doppler ultrasound³⁵ (LOE 2).

Testicular asymmetry is a major indication for varicocelectomy among the pediatric age group. Patients showing a persistent discrepancy of more than 20% between the right and left testes size over a period of 12 months should be considered for surgical intervention³⁶ (LOE 1). One study showed significant decreased sperm concentration and total motile sperm count when there was a persistent testicular size discrepancy greater than 20% between the normal and affected testis³¹ (LOE 2).

A pre-operative period of observation is recommended to determine if the asymmetry resolves, persists, or progresses. Peak retrograde flow determination via scrotal Doppler ultrasonography is a valuable tool to predict persistent, progressive, and new onset asymmetry. A high peak retrograde flow of greater than 38 cm/s with 20% asymmetry predicts persistent and worsening testicular asymmetry.³⁷ Patients presenting with pain in pediatric varicocele have a significantly higher peak retrograde flow³⁸ (LOE 2).

Varicoceles occur in 15% of adolescent males and are generally considered to be an extratesticular phenomenon. Intratesticular varicocele is a rare entity, characterized by dilatation of intratesticular veins. It is found in up to 2% of adolescent varicocele. Adolescents with intratesticular varicocele in association with testicular asymmetry will develop worse asymmetry over time and should be scheduled for surgery rather than followed.³⁹

8.1.5 **Management strategies, including operative techniques**

8.1.5.1 **Open surgery technique**

Open surgical correction of varicoceles has been done using the Palomo or Ivanisevich technique. With the advent of microsurgery, magnification has been introduced to refine the dissection. Additionally, venography and lymphangiography have been used in several techniques.

One study has shown open Palomo varicocelectomy persistence rates in 2.2% of patients and hydrocele development in 8.6% of patients.⁴⁰ Similar hydrocele rates (7.69% and 2.2%) were seen by Bolla *et al.*⁴¹ and Kraeft *et al.*, respectively.⁴² Okuyama *et al.* showed that pre-operative testicular atrophy decreased after surgery in 9 out of 16 patients⁴³ (LOE 2). In those patients who underwent observation only, 8 patients had testicular atrophy at the initial visit, but 12 had atrophy after follow up. Kass and Marcol compared 3 open techniques: modified Ivanisevich, modified Palomo, and standard Palomo.⁴⁴ They showed that standard Palomo had significantly better results compared to the artery-sparing techniques (LOE 2). The Ivanesevich approach has been noted to have recurrence rates ranging from 0% to 10%.^{45,46} Adding an incision of the tunica vaginalis has shown some benefit. Tsikopoulos *et al.* showed that incision of the tunica vaginalis prevented hydrocele occurrence⁴⁷ (LOE 2). Cimador *et al.* also noted a lower incidence of hydrocele if the tunica was either resected or everted.⁴⁸

Microsurgery has been applied during the subinguinal and retroperitoneal techniques. In a comparison of different degrees of magnification in 100 patients divided in 3 groups (microscope, loupes, and no magnification), there were no recurrence or hydrocele formation in the microscope group; the highest rates were seen in the no magnification group⁴⁹ (LOE 2). With microsurgery, hydrocele rates are noted to be lower than in regular open techniques. Schiff *et al.* noted a hydrocele rate of 1%.⁵⁰ Microsurgery with sparing of artery and lymphatics showed a temporary hydrocele, which then completely resolved, in 1 out of 32 patients. There were no recurrences^{51–53} (LOE 2). Using microsurgical repair in boys, catch-up growth was noted in 65% of testes.⁵⁴ At 1-year follow-up, 1 patient (1.6%) had recurrence and no patients had hydrocele formation (LOE 2). In another study, catch-up growth began 9 months post-operatively and became significant 12–24 months post-operatively.⁵⁵ Left versus right testicular volume differences initially noted to be significant were insignificant at the end of the study (LOE 2). However, in a study by Spinelli *et al.*, a spontaneous catch-up growth of 29.6% was seen in an observation group compared to 85.2% in the lymphatic-sparing varicocelectomy group,

suggesting the need for close follow-up post-surgery.⁵⁶ Microscopic retroperitoneal lymphatic-sparing varicocelectomy has been shown to have no recurrences and no hydrocele⁵⁷ (LOE 2). Lymphatic preservation using isosulfan blue was studied by Schwentner *et al.* in 50 boys randomized into 2 groups: standard microsurgery and standard microsurgery with additional isosulfan blue.⁵⁸ While no hydroceles were noted in the isosulfan group, the number of recurrences was similar in the 2 groups (LOE 1).

Microsurgical anastomosis of the spermatic vessels to the inferior epigastric vessels has been studied in several papers. This approach has shown similar rates of recurrence and hydroceles as the other open techniques. Camoglio *et al.* observed a 3% recurrence and hydrocele rate.⁵⁹ Similarly, Lima *et al.* showed a 3% recurrence rate using microsurgical anastomosis.⁶⁰ A larger study by Feber and Kass. with 312 patients, showed a persistence rate of 3.9% and a 5% significant hydrocele rate that required surgery.⁶¹

Venography has been studied in the open approach. This technique allowed the visualization of collateral drainage in 12% to 16% of patients,^{62,63} which was corrected intra-operatively^{62,64} (LOE 2). Procedures using venography have likewise shown a 1.7% hydrocele rate and testicular atrophy in 1 of 172 patients.⁶⁵

8.1.5.2 Sclerotherapy/Embolization/Combined techniques

Embolization of the gonadal vein has been used in both primary and failed varicocele surgery⁶⁶ (LOE 2). Success rates vary from 65% to 95%.⁶⁷⁻⁷⁰ One study showed a success rate of 68.6% after the first try and 88% success after a second or repeat embolization.⁷¹ The effect of embolization on catch-up growth was studied in 30 patients, 14 of whom had significantly smaller left testes.⁷² On follow-up, 12 patients exhibited an increase in left testicular size (LOE 2).

A study of the radiation dose during embolization showed that the average dose was 8.8 mSv.⁷³ The total average risk of a fatal cancer induction was 0.16% and risk for hereditary defects was 0.0007%. The maximum skin dose was 250 mGy, which was far below the 2 Gy threshold for deterministic effects. The recurrence rates of embolization, however, can be high when compared to other procedures. Ayechu-Diaz *et al.* studied percutaneous embolization compared to laparoscopy using a control group.⁷⁴ There were 66% recurrences in the embolization group and none in the laparoscopic Palomo group. However, 1 patient in the embolization group later underwent hydrocele surgery (LOE 2).

Sclerotherapy alone for varicocele management has also been studied. Zaupa *et al.* showed a low persistence of 7.1% and no recurrence after a second therapy.⁷⁵ However, 1 patient had scrotal hematoma together with focal testicular necrosis post-surgery. Ficarra *et al.* also observed a low persistence rate of 2.2% using sclerotherapy⁷⁶ (LOE 2). Long-term follow-up after 2 years showed a success rate of 92%, with an 8% recurrence rate. Thon *et al.* showed hydrocele rates of 6.2% using sclerotherapy⁷⁹ (LOE 2).
The combination of sclerotherapy followed by embolization has also been extensively studied. The procedures usually involve initial sclerotherapy with a sclerosing agent such as sodium tetradecyl sulphate⁸⁰ or sodium tetradecyl sulfate foam⁸¹ (LOE 2). If feasible, this is immediately followed by embolization with coils. Spasms of the veins and collaterals can diminish success⁸² (LOE 2). The success of the combined procedure has ranged from 79.4% to 95%⁸⁰⁻⁸⁵ (LOE 2).

Sclerotherapy has also been incorporated in open surgery, using sodium morrhuate or 3% polidocanol. Lebed *et al.* observed an overall recurrence rate of 2.7% in patients receiving combined surgical ligation and sclerotherapy ablation.⁸⁶ Patients who underwent the loupe-assisted subinguinal approach had the best results, with no varicocele recurrences or hydroceles formation. Using sclerotherapy, Carmignani *et al.* observed 1 hydrocele in 25 patients after a 6-month follow-up⁸⁷ (LOE 2).

8.1.5.3 Laparoscopic varicocelectomy

Laparoscopic varicocelectomy has been very well studied. Recurrence rates have been very good, with some studies showing no recurrences.⁸⁸ Hydrocele recurrence after laparoscopic varicocelectomy has been variable, however. No hydroceles were noted by Urbanowicz and Górniak.⁸⁹ And though Belloli *et al.* showed only one recurrence and one hydrocele in 80 patients,⁹⁰ Keys *et al.* observed a 12.5% hydrocele rate in 24 patients.⁹¹

Using the laparoscopic Palomo technique, Méndez-Gallart *et al.* had a 13% hydrocele rate, 9% of which required surgery⁹²; their earlier study had a 13.5% hydrocele rate at 10 years' follow-up.⁹³ The laparoscopic approach has also been studied following inguinal surgery in 44 patients; 1-year follow-up showed no testicular atrophy, and all affected testes showed stable size or an increase in growth⁹⁴ (LOE 2). Hassan *et al.* noted a higher rate of hydroceles (22.8%) using laparoscopic varicocelectomy.⁹⁵ There was a significantly higher rate of hydroceles formation (31.1%) if the vessels were ligated and divided versus just ligated (11.8%).

The retroperitoneoscopic approach has been shown to have no recurrence at 2 years' follow-up.⁹⁶ Cobellis *et al.* studied the same approach in 97 children, of which 17.6% needed elective conversions to a transperitoneal approach.⁹⁷ The persistence rate was 11.2% and the hydrocele rate was 6.2%.

Sparing and non-sparing of the testicular artery has been studied, with varying results. Some studies showed no difference in recurrence rates between preservation or non-preservation of the artery⁹⁸⁻¹⁰⁰ (LOE 2, LOE 4). Cohen studied artery preservation in 40 boys and showed a 12.5% hydrocele rate.¹⁰¹ Furthermore, 70% of the patients had a post-operative increase in testicular volume (LOE 2). One study showed a lower recurrence rate (1.6%) with artery and lymphatic preservation¹⁰² (LOE 2).

Two studies showed lower recurrence rates with non-preservation of the artery. In a prospective, multicentre study with 90 cases, Varlet *et al.* showed that the recurrence rate was 32.1% in the artery-sparing group versus 8.4% in the non-artery sparing group¹⁰³ (LOE 1). The laparoscopic Palomo approach also had a lower recurrence rate (2.2%) versus artery-sparing (3.5%)¹⁰⁴ (LOE 2). However, 9 patients who underwent the Palomo technique had hydroceles. Patients undergoing the Modified Palomo approach have shown higher sperm concentration per milliliter, sperm motility, volume, vitality, and normal forms¹⁰⁵ (LOE 2). Colour Doppler ultrasound prior to laparoscopic Palomo

varicocelectomy has helped identify and ligate refluxing deferential veins, resulting in no recurrences after 2 years¹⁰⁶ (LOE 2). The Trendelenburg position has also been used to identify collaterals and improve success.^{107,108}

Different sealing and ligation instruments have also been studied, including clips, electro sealing devices, ultrasonically activated scalpels, and electrocoagulation. In one study, clips were compared to a vascular sealing device (LigaSure[™]) in 122 patients.¹⁰⁹ While there was 1 recurrence in the LigaSure group, the hydrocele rate was similar in both groups (LOE 2). Another study using the LigaSure device showed 11 of 16 patients to have catch-up growth, with 2 patients developing post-operative hydroceles.¹¹⁰ In their study, Sasagawa *et al.* noted that the ultrasonically activated scalpel was safe in 10 patients.¹¹¹ Clips have also shown to have lower persistence (3.4%) and hydroceles (13.8%) than electrocoagulation (10.5% and 23.7%, respectively).¹¹²

The importance of lymphatics in determining the occurrence of hydroceles has been well studied. A meta-analysis of 127 studies by Liang *et al.* compared lymphatic-sparing laparoscopic varicocelectomy (LSV; 489 cases) to lymphatic non-sparing laparoscopic varicocelectomy (LNSV; 307 cases) and found that the hydrocele rate in LSV was significantly lower than in LNSV.¹¹³ The recurrence rates, however, were similar and catch-up growth was seen in both groups. Lymphatic sparing laparoscopic varicocelectomy is valuable in reducing post-operative hydrocele (LOE 1). Kocvara *et al.* compared the laparoscopic non-lymphatic sparing approach to the microsurgical lymphatic sparing approach and showed that the microsurgical approach had significantly lower hydroceles (1.9%) and testicular hypertrophy (2.9%) than the laparoscopic non-lymphatic sparing approach has shown to have higher hydrocele rates than lymphatic sparing, non-artery sparing techniques^{115,116} (LOE 2).

Lymphangiography to decrease hydrocele occurrence post-operatively has also been studied. Isosulfan blue is usually given to delineate the lymphatics. Chiarenza *et al.* showed no recurrences and no hydroceles after lymphography in 27 patients¹¹⁷ (LOE 2). Lymphography and laparoscopic varicocelectomy only was compared by Schwentner *et al.* in a randomized prospective trial with 50 patients.¹¹⁸ They found no hydroceles in the lymphography group and 20% hydroceles in the laparoscopy only group. Recurrence rates were similar for both groups (LOE 1). Golebiewski *et al.* showed similar results in a study with 52 boys, with no recurrences or hydroceles in the lymphatic-sparing group, but four hydroceles in the lymphatic non-sparing group¹¹⁹ (LOE 2). Similar patterns were seen in the studies of Glassberg *et al.*¹²⁰ and Tong *et al.*¹²¹ (LOE 2). Lymphography has also been used in the retroperitoneoscopic approach with good success¹²² (LOE 2). D'Alessio *et al.* compared lymphatic mapping with methylene blue in several surgical approaches to a control group with no mapping.¹²³ They found that there were fewer post-operative hydroceles in the mapping patients versus controls (2.1% versus 6.4%, respectively).

Variations of standard laparoscopic techniques have been studied in relation to varicocelectomy. Needle laparoscopic varicocelectomy has been described by Xie *et al.* with no recurrences on 1-year follow-up.¹²⁴ The two-trochar approach has had variable success. Link *et al.* showed no recurrences using two trochars and harmonic scalpel¹²⁵ (LOE 2). Mendez-Gallart *et al.* used two ports and the LigaSure in 63 boys and had a 14% hydrocele rate after 1.8-years follow-up¹²⁶ (LOE 2). Laparoendoscopic single-site varicocelectomy has also been the subject of many papers, which showed no recurrences,

minimal to no hydroceles, and no complications^{127,128} (LOE 2). Laparoendoscopic single-site varicocelectomy has also been found to be safe in post-embolization patients.¹²⁹ Hidalgo-Tamola *et al.* studied robotic-assisted laparoscopic varicocelectomy (RALV) in four patients compared to two agematched controls and found RALV to have no intra- or post-operative complications.¹³⁰

8.1.5.4 **Comparison of Laparoscopic, Open surgery, and Sclerotherapy**

Laparoscopic varicocelectomy has been studied in comparison to open surgery. A randomized controlled trial by Podkamenev *et al.* investigated the Palomo lymphatic-sparing approach in laparoscopy and open inguinal surgery.¹³¹ Hydroceles were significantly less in the laparoscopy group (0.23%) versus the open group (1.82%). Relapse rates were not significantly different. Laparoscopy also showed less wound complications and edema, as well as shorter hospital stays, operative times, and post-operative analgesia^{131,132} (LOE 1, LOE 2). Barroso *et al.* conducted a systematic review comparing open Palomo (496 patients) to laparoscopic Palomo (1344 patients).¹³³ No significant difference was found for either hydrocele occurrence (9.7% for open Palomo versus 6.9% for laparascopic Palomo) or recurrence rates (2.99% versus 4.4%, respectively). When the Palomo was classified as either Classic or Modified, the hydroceles were significantly higher in the classic Palomo technique. Recurrences and catch-up growth were similar for open and Modified Palomo (LOE 1).

A meta-analysis by Borruto *et al.* compared laparoscopic versus open varicocelectomy in 11 studies.¹³⁴ They found no statistical difference in recurrence or hydrocele rate. In the laparoscopic group, there was a higher recurrence in the artery only ligation versus artery and vein ligation. Laparoscopic varicocelectomy was advantageous in bilateral cases (LOE 1). A 10-year review of 92 patients by Diamond *et al.* showed that laparoscopic varicocelectomy had the highest success (100%) compared to Palomo, microsurgical subinguinal, and Ivanisevich varicocelectomy (93%, 88%, and 69%, respectively).¹³⁵ Hydroceles were lowest in the microsurgical approach (0%) and highest in the laparoscopic group (32%).

In a study comparing several techniques, Riccabona *et al.* showed that the Modified Palomo technique had the lowest recurrence rate (2%) and no hydroceles, which was better than the standard Palomo, inguinal, and laparoscopic approaches.¹³⁶ Laparoscopic lymphatic-sparing varicocelectomy was compared to microsurgical varicocelectomy over a 2-year period.¹³⁷ The laparoscopy group had 1 hydrocele and the microsurgical group had 1 recurrence. Both techniques were comparable in preventing recurrences and hydroceles.

A comparison of laparoscopic and subinguinal varicocelectomy showed a higher incidence of hydroceles in the subinguinal group unless the tunica vaginalis was excised and everted; however, 75% of patients exhibited catch-up growth regardless of technique.¹³⁸ A study of 3 techniques (laparoscopy, Palomo, and inguinal) showed that the inguinal approach had no recurrences or surgical hydroceles.¹³⁹ Laparoscopy and Palomo showed similar rates for recurrence and hydroceles. Two other studies compared laparoscopic varicocelectomy and open surgery. Moreira-Pinto *et al.* noted similar hydrocele rates, but with significantly higher recurrence in the open approach.¹⁴⁰ Niyogi *et al.* noted that laparoscopy had a higher incidence of hydrocele, but not significantly¹⁴¹ (LOE 2). They also observed that increasing age significantly decreased recurrence. Colour Doppler ultrasound has been used in conjunction with different operative techniques. Its use resulted in no recurrences, regardless of whether laparoscopy or open techniques were used.¹⁴² Sclerotherapy was compared to other techniques. Pintus *et al.* compared it to open inguinal, open modified Palomo, laparoscopic Palomo, and classic Palomo.¹⁴³ The lowest recurrence rate was seen in the original Palomo operation; all other techniques, including sclerotherapy, had similar recurrences (LOE 2). A comparison of sclerotherapy and open Palomo showed the same recurrence rate of 4.5%, with hydroceles only seen in open surgery.¹⁴⁴ Sclerotherapy was shown to be simpler, cheaper, and without hydrocele formation.

8.1.5.5 **Conservative management/observation only**

Conservative management or observation over time was studied as a form of varicocele management. Preston *et al.* retrospectively studied 33 boys with varicocele: 30 were observed over time and 3 underwent surgery for pain and increasing testicular discrepancy.¹⁴⁵ Of the patients with volume differentials of 20% or more. 50% experienced catch-up growth over time. Although some boys may be managed by observation, surgery is indicated if there is an increasing volume differential. Kolon *et al.* also did a retrospective study of 71 boys followed over 2 years with ultrasound.¹⁴⁶ At the end of study, 85% of the patients had normal volume differentials (<15% discrepancy) compared to 54% at the start of the study. The authors recommended two to three yearly ultrasounds to accurately establish testicular volumes.

8.1.6 **Post-operative consequences and paternity**

8.1.6.1 **Catch-up growth**

Li *et al.* conducted a meta-analysis of the effect of varicocelectomy on testicular volume and catch-up growth.¹⁴⁷ In the combined analysis of 14 studies (1475 patients), there was a significant reduction in testicular volume discrepancy after surgery in the $\geq 10\%$ and the $\geq 20\%$ discrepancy groups. The number of patients with volume discrepancies significantly decreased, and average catch-up growth was 76.4%. There is a clear advantage of surgery when the discrepancy is $\geq 10\%$. Paduch and Niedzielski conducted a randomized controlled trial on varicocelectomy and observation over 12 months.¹⁴⁸ Varicocelectomy resulted in a decrease of mean atrophy index from 12.7% pre-operatively to 3% post-operatively. Surgery also led to a greater increase in left testicular volume of 26% versus 11% in the controls within 12 months of repair (LOE 1). Post-operative catch-up growth has also been seen in several other studies. Cayan *et al.* found a 53% catch-up growth rate,¹⁴⁹ while Messina *et al.* found 81.5% catch-up growth in 66 patients who underwent either laparoscopic or open varicocelectomy.¹⁵⁰

Artery preservation was studied by Zampieri *et al.* in laparoscopic varicocelectomy and micro-inguinal varicocelectomy in 465 patients with an 18-month follow-up.¹⁵¹ They found that 45% of the laparoscopic group and 34% of the micro-inguinal group had equal testicular volumes, and 32% of all patients had complete and real catch-up growth. Lund *et al.* found that artery preservation in laparoscopic varicocelectomy did not affect catch-up growth.¹⁵² In one study, preservation of lymphatics also did not influence catch-up growth in 136 patients followed over 24.7 months; no significant difference was seen between the varicocelectomy with and without lymphatic preservation groups.¹⁵³ Gershbein *et al.* found that ipsilateral testicular hypertrophy after varicocelectomy is not dependent on age or type of repair.¹⁵⁴ A history of prior inguinal surgery was studied by Woldu *et al.* in 22 boys, all with a history of previous inguinal operation.¹⁵⁵ Here, 22 boys underwent laparoscopic or open varicocelectomy and were followed for 24.2 months. There was a decrease of testicular asymmetry from 27.6% to 10.5%, and an incidence of catch-up growth of 43%, with no difference between artery-sparing and non–artery-sparing.

The use of colour Doppler ultrasound in post-varicocelectomy follow-up of boys is recommended over just a regular physical exam.¹⁵⁶

8.1.6.2 Hydroceles

Hydroceles may occur between 1 week and 44 months following surgery, with a median of 2 months.¹⁵⁷ Misseri *et al.* found that hydroceles occur more often after a Palomo repair (28%) compared to the Ivanissevich procedure (14%).¹⁵⁸ The incidence of hydroceles was also found to be higher in open surgery compared to laparoscopic surgery, in bilateral cases, and in non-lymphatic sparing surgery. Tunica vaginalis eversion also led to a lower hydrocele rate compared to excision.¹⁵⁹ This finding was likewise observed by Castagnetti *et al.*, who studied preemptive hydrocelectomy.¹⁶⁰ They also found significantly less hydroceles in the excision/eversion group (4.3%) compared to patients with intact tunica (13%).

8.1.6.3 Nerve injury post lap varicocelectomy

The most common type of nerve injury in laparoscopic varicocelectomy is along the distribution of the genitofemoral nerve, which resolves in 6–9 months.¹⁶¹ Injury was also more common when using ultrasonic shear compared to clips.¹⁶²

8.1.6.4 Vascular issues in varicocelectomy

Post-operative sequelae that involve vascular issues are usually recurrences. In a study of 19 redooperations with a 23.4-month mean follow-up, distal collateral veins were the cause of the redo operation.¹⁶³ Persistent intra-operative findings were large veins within the cord, just proximal to the junction with the vas and in continuity with the dilated veins distal to the internal ring. Recurrence was also attributed to shunt and stop-type varicoceles. Some were operated if the discrepancy was \geq 20%; if the discrepancy was less, they were observed. The observed group had a higher risk of developing asymmetry. Those who underwent an inguinal approach with ligation of the internal and external spermatic veins showed lower recurrence (6.3%) compared to the retroperitoneal approach (30.8%)¹⁶⁴ (LOE 1).

8.1.6.5 **Semen and other parameters post varicocelectomy**

There have been several studies that looked into sperm and laboratory parameters post varicocelectomy. Fisch *et al.* found an increased follicle-stimulating hormone (FSH) baseline level and FSH response to gonadotrophin-releasing hormone (GnRH) after surgery.¹⁶⁵ Hienz *et al.* observed that testicular biopsies performed in boys undergoing varicocelectomy showed the same adult changes, though in less severe form.¹⁶⁶ The authors recommended surgery at the time of varicocele diagnosis. Spermiograms were studied in 50 children who underwent early varicocelectomy.¹⁶⁷ Of these patients, 21 were re-assessed at ages 20 to 29 years, and three recurrences and three hydroceles were found. Patients who underwent early surgery had better spermiograms than the control group. In another study, 75 of 200 adolescents who underwent varicocelectomy were re-evaluated at age 21 and compared to controls.¹⁶⁸ Abnormal spermiograms were seen in 46.7% of the early surgery group compared to 56% for unoperated controls. The authors recommended early surgery in adolescence to maintain fertility potential. Lenzi *et al.* followed 19 adolescents who underwent varicocelectomy for 2 to 8 years after surgery.¹⁶⁹ They were compared to controls with and without varicoceles. The study group had a significantly lower sperm concentration than controls, but higher sperm motility and morphology mean values compared to the unoperated group.

8.1.7 **Prevention of PV**

Early recognition and treatment of a severe varicocele with testicular hypotrophy may help prevent the infertility associated with this condition¹⁷⁰ (LOE 2). Prevention of varicoceles is still under investigation. Some studies suggest a role for flavonoids. Micronized purified flavonoid fraction (MPFF) is a phlebotropic drug commonly used to treat the signs and symptoms associated with chronic venous insufficiency. The use of bioflavonoids in patients with subclinical varicocele could reduce the development of palpable varicocele. In a murine model, MPFF was found to have favourable effects on the regressions of testicular damage secondary to varicocele.¹⁷¹ However, bioflavonoids did not show any protective factor against testicular growth arrest.¹⁷²

8.1.8 **Recommendations**

Varicoceles occur in 14% to 16.5% of adolescents, who are more likely to have abnormal spermiograms. Brothers of patients have a 4.5-fold significantly greater incidence of varicoceles and should be evaluated (GOR C)

Colour Doppler ultrasound should be included in the evaluation of pediatric varicoceles (GOR C)

Persistent testicular asymmetry of ≥20% in the presence of a varicocele warrants surgical intervention (GOR C)

There are several surgical techniques that have been studied, including open surgery, microsurgical open surgery, laparoscopy, sclerotherapy, and embolization. These techniques have been assessed in terms of recurrence, hydrocele rates, catch-up growth, and complications. The different techniques have varying recurrence rates and hydrocele rates (GOR B)

Surgery shows better results over observation in terms of catch-up growth and testicular volume. Post-operative spermiograms show better results compared to pre-operative values (GOR C)

8.2 Micropenis, Buried Penis, and Webbed Penis

8.2.1 Introduction

There are several conditions that make the penis look tiny and small. A concealed penis could be secondary to a short penile shaft, often termed micropenis. But more commonly, this inconspicuous appearance is secondary to other causes, including penoscrotal webbing or a megaprepuce, developmental conditions like prepubic fat tissue that overhang the penis, or iatrogenic causes like a trapped penis due to adhesions following circumcision.

8.2.1.1 **Methods**

A systematic review was performed in PubMed without time limitation, owing to the scarcity of literature. Key words were micropenis, buried penis, trapped penis, and webbed penis with limit child. There were 468 articles for micropenis, 70 for buried penis, and 18 for webbed penis. The majority of papers were case reports; 11 were used for Micropenis and 6 for buried penis. The studies were then assessed according to the different levels of evidence and grades of recommendation following the ICUD Grades of recommendation and Levels of Evidence.

8.2.2 Micropenis

The term micropenis refers to a penis that is normally formed but abnormally small (**Figure 8-3**). Typically, the ratio of the length of the penile shaft to its circumference is normal. Micropenis is defined as a penis with a stretched length more than 2.5 standard deviations less than the mean for age¹⁷³ (LOE 2). This condition may be considered a minor form of ambiguous genitalia with correlated medical and psychological problems, similar to those of the major disorders of sex development form.

FIGURE 8-3 Micropenis. (Photo provided courtesy of Dr. K. Narasimhan, KK Women's and

Children's Hospital, Singapore.)



Micropenis results from a multiplicity of endocrine and non-endocrine conditions. The most common etiologies include hypogonadotropic hypogonadism (hypothalamic or pituitary failure), hypergonadotropic hypogonadism (testicular failure), and idiopathic micropenis¹⁷⁴ (LOE 2). As an abnormality in the production or effect of testosterone results not only in a small penis but usually in hypospadias as well, a true micropenis often seems to be a consequence of a deficiency of gonadotropic

hormones. Therefore, micropenis results from a hormonal abnormality that occurs after 14 weeks of gestation. Gonadotropin-releasing hormone and/or human chorionic gonadotrophin (hCG) stimulation tests may be helpful in defining the etiology¹⁷⁵ (LOE 2).

In patients with micropenis, the scrotum is usually normal, but the testes often are small and undescended. In a few cases, the corpora cavernosa are severely hypoplastic. It is important to use a standard technique of stretched penile measurement and nomograms for age to identify children with micropenis (Table 8-1; LOE 2).^{173,175,176} All children aged older than 1 year with a stretched penile length of less than 1.9 cm need evaluation¹⁷³ (LOE 2).

Age	Mean ± SD	Mean – 2.5 SD		
Newborn, 30 wk	2.5 ± 0.4	1.5		
Newborn, 34 wk	3.0 ± 0.4	2		
0-5 mo	3.9 ± 0.8	1.9		
6-12 mo	4.3 ± 0.8	2.3		
1—2 у	4.7 ± 0.8	2.6		
2—3 у	5.1 ± 0.9	2.9		
3—4 у	5.5 ± 0.9	3.3		
4—5 у	5.7 ± 0.9	3.5		
5—6 у	6.0 ± 0.9	3.8		
6—7 у	6.1 ± 0.9	3.9		
7—8 у	6.2 ± 1.0	3.7		
8—9 у	6.3 ± 1.0	3.8		
9—10 у	6.3 ± 1.0	3.8		
10—11 y	6.4 ± 1.1	3.7		
Adult	13.3 ± 1.6			
Source: Lee PA Mazur T. Danich P. et al. 174- Foldman KW, and Smith DW/176: and Calikagly AS 177				

TABLE 8-1 Stretched penile length table

Source: Lee PA, Mazur T, Danish K, *et al*.¹⁷⁴; Feldman KW, and Smith DW.¹⁷⁶; and Calikoglu AS.

The differentiation of different forms of micropenis by this measurement is extremely important, particularly differentiating the buried penis in the obese infant or the penis concealed by an abnormal skin attachment.

Very rarely, castration and gender conversion can be considered in individuals with microphallus who are insensitive to and rogens. In most patients with micropenis, male gender assessment can be maintained with androgen stimulation^{177,178} (LOE 2). The role of testosterone imprinting and later gender identity would need to be considered.

The clinical management of micropenis has been contentious, with disagreement regarding the capacity of testosterone treatment to induce a functionally adequate adult penis. No general consensus exists regarding dosage, method of administration, timing, or duration of androgen treatment. In patients with testicular failure and proven androgen sensitivity, androgen therapy is recommended during childhood and at puberty to stimulate the growth of the penis176,179–182 (LOE 3). The most common therapeutic regimen is testosterone enanthate 25–50 mg intramuscularly once a month for 3 months. Some physicians also use testosterone cream, but its absorption is variable and not easily controllable¹⁸³ (LOE 2).

8.2.3 Buried and Webbed Penis

A buried penis is hidden below the preputial skin (**Figure 8-4**). This may be the result of excessive fat in the prepubic area of the anterior abdominal wall or lack of anchoring of the superficial fascia and skin to the deeper fascia at the base of the penis. The outcome will be such that the penile skin will not be covering the penile shaft properly along its length, and the shaft will become invisible and stay hidden under skin^{184,185} (LOE 2,4).

FIGURE 8-4 Buried penis in adolescent male.

(Photo provided courtesy of Dr. A. Jacobsen, KK Women's and Children's Hospital, Singapore.)



Abnormal bands between Scarpa's fascia and Buck's fascia binding the penis have been shown to not properly attach the penile skin to the shaft of penis.

Excessive preputial skin, megaprepuce, is another entity where the penis looks buried under a large amount of foreskin. Large scrotal masses like hernias and/or hydroceles may also bury the penis.

Webbed penis is the result of abnormal Dartos bands anchoring the penile skin on the surface of the scrotum. Consequently the ventral penoscrotal angle is demolished, resulting in the appearance of a short penis. It can exist in isolation but may also occur with hypospadias, chordee, and micropenis. The cosmetic appearance is often unacceptable, and hence, requires surgical correction.

Trapped penis is an acquired form of buried penis. The penile skin after circumcision may form a circumferential scar distal to or at the level of the glans, trapping the penis within the scar embedded in prepubic fat or scrotum.

Physical examination of the genitalia will show the buried penis with an excessive presence of prepubic fat, which is hanging over the base of the penis. This is more commonly seen in older children and obese adolescents. When the excessive fat tissue is pressed down, the normal size of the penis can be clearly demonstrated to the parents and the patient.

Lifting up of scrotal skin when the penis is moved to lie flat on the anterior abdominal wall can show the webbed penis. The penoscrotal fusion could extend from the preputial skin to the scrotal wall and the penile skin is lost on the ventral aspect of the penis. It is important to rule out the presence of hypospadias and chordee.

While many prepubertal children with a buried penis secondary to excessive suprapubic or prepubic fat will not need surgical correction, a webbed and trapped penis may require surgical intervention (**Figure 8-5**).

FIGURE 8-5

Buried penis post-surgery.

(Photo provided courtesy of Dr. A. Jacobsen, KK Women's and Children's Hospital, Singapore.)



Most buried penises will become normal with the loss of the excessive fat pad with growth and become normal by puberty. In excessively obese individuals who are postpubertal, surgical correction may be needed to ensure psychological confidence. Liposuction has been helpful in severe cases. Abdominoplasty (including a V-Y plasty) and suprapubic lipectomy have been reported in the literature and may be needed in extremely rare instances¹⁸⁶ (LOE 4).

The surgical procedure should include degloving of the penis to its base and fixing the penile skin and Dartos fascia to the deeper fascia to re-establish the penopubic angle and the penoscrotal angle¹⁸⁷ (LOE 2).

In a webbed penis, penile skin can be created by a transverse incision across the penoscrotal web and closing it in a vertical manner, thus using the Heinecke-Mikulicz principle to repair webbed penis¹⁸⁸ (LOE 4).

Although application of topical steroids may be helpful in some cases of a trapped penis, the majority will require surgical correction¹⁸⁹ (LOE 4).

8.2.4 **Recommendations**

In a patient with micropenis, buried penis, or webbed penis, careful physical examination is of utmost importance.

All boys of 1 year of age with a stretched penile length less than 1.9 cm should be further investigated for conditions associated with micropenis.

Most boys with micropenis should be raised as males and can have normal sexual intercourse. (GOR A)

Boys with a buried penis before puberty do not need surgical correction.

8.3 Penile Torsion

8.3.1 Introduction

Congenital penile torsion is a malformation in which there is a three-dimensional malrotation of the corporal bodies or sometimes just the glans¹⁹⁰ (LOE 2). It is often accompanied with chordee or hypospadias, and these cases may have abnormal development of the corpus cavernosum^{191,192} (LOE 2, LOE 4). Pierrot and Muthurajan collected 370 male infant candidates for circumcision and showed that 105 had isolated neonatal penile torsion, with an incidence of 27%.¹⁹³ The torsion was to the left in 99% of the cases (LOE 2). The true incidence of this anomaly is unknown, as most children are asymptomatic except for cosmesis. Shaeer reported that 12% of 11,340 adult patients who came to the infertility or sexual dysfunction clinic had penile torsion.¹⁹⁴ The direction of torsion was clockwise in 35% and counterclockwise in 65%. The degree of torsion in the flaccid state was mild (5–30 degrees) in the majority of the cases (80%), moderate (30–60 degrees) in 15%, and severe (more than 60 degrees) in 5% (LOE 4). The difference between neonates and adults in direction of torsion is unknown. No patient complained of sexual dysfunction related to penile torsion (LOE 4), although the parents of affected children are often concerned about the future sexual dysfunction.

8.3.1.1 Materials and methods

Previously published literature in English and the available international literature were retrieved through a MEDLINE search using 2 keywords: penile torsion and torsion of penis. Predetermined criteria for inclusion consisted of focus on the congenital penile torsion and any procedure referring to the repair of penile torsion. The search yielded 67 articles between 1955 and 2013. Of these, 15 articles referred to penile torsion with hypospadias, and 3 articles referred to penile torsion with the exstrophy-epispadias variant. The cases with congenital isolated penile torsion were few in number; 28 articles were related to the surgical procedures. Summaries of articles were reviewed with the full text of the relevant article. Of these, 8 were included for this section. The studies were

assessed according to levels of evidence and ICUD grading was applied. The majority of publications were case reports and case series. Thus, published literature appears not to be evidence based. The LOE was 2–4; the grade of recommendation will be C at best.

8.3.2 Surgical correction

Surgical correction is not considered in cases with mild torsion. For pediatric patients with isolated penile torsion more than 60 degrees, some surgical techniques have been published and would be familiar for pediatric urologists who practice hypospadias repair regularly.

In the mild forms of penile torsion (<90 degrees), the glans is directed away from the midline, but the orientation of the corporal bodies at the base of the penis is usually normal. Thus the defect is correctable by penile degloving and realignment of the median raphe^{190,192} (LOE 2, 4). For more severe penile torsion (>90 degrees), Fisher and Park reported dorsal Dartos flap rotation¹⁹¹ (LOE 2). In this technique, a dorsal Dartos flap is rotated around the right side of the penile shaft to correct the rotation to the left. Bauer and Kogan replicated the procedure in 25 children with at least 60 degrees penile torsion; 16 children showed complete resolution, and 7 had mild residual torsion less than 10 degrees¹⁹² (LOE 4). Shaeer reported degloving with skin realignment for 8 adults and the Dartos flap technique for another 8 adults.¹⁹⁴ Full correction was achieved in all cases (LOE 4). Snow reported on diagonal placation. If the penile torsion persisted by the artificial erection after degloving, a diagonal placating suture was taken parallel to the neurovascular bundle on the right corporal cavernous body and the opposite half of the suture was taken parallel to the neurovascular bundle more proximally on the left corporal, and these sutures were tied to correct the torsion (195) (LOE 4). Zhou et al. reported 11 pediatric patients whose torsion was corrected by suturing the lateral edge of the corpus cavernosum to the pubic periosteum¹⁹⁶ (LOE 4). Aldaqadossi et al. reported a prospective randomized study comparing the dorsal Dartos flap to suturing the tunica albuginea to the pubic periosteum.¹⁹⁷ They found no apparent differences between these methods; however, the Dartos flap technique may be easier to perform (LOE 1)

8.3.3 **Recommendations**

Mild forms of penile torsion do not need surgical correction.

Milder and severe forms of penile torsion can be managed by the usual techniques used in hypospadias correction with penile torsion.

It is recommended to report penile torsion in a standardized way: X degrees of torsion to the left/right, with the 6 o'clock position as 0 degrees.

8.4 **Diphallia**

8.4.1 Introduction

Diphallia (penile duplication) is a rare anomaly that occurs in every 5 million live births. Most reported cases of diphallus occurred in patients with bladder or cloacal exstrophy; the diphallus without exstrophy variant is extremely rare. Diphallia is often accompanied with various other anomalies, such as double bladder, double urethra, and rectal atresia. Diphallia was reported as a symptom in the caudal duplication syndrome, and in this cluster, diphallia is associated with various duplication variants of the lower digestive tract, including anus, rectum, sigmoid, or descended colon^{198–207} (LOE 4). Some cases of diphallus have 2 sets of corpora cavernosa, but the majority of them have a single corpus cavernosum in each phallus (**Figure 8-6**). The number of phallic corpora cavernosa and their relationship to the corpora spongiosa and the ramus would be important information to understand the classification, but this is not always reported.

Schneider classified this anomaly as

- Duplication of the glans only
- Bifid or incomplete diphallia with a single corpus cavernosa in each phallus
- Complete diphallia with each penis having two corpora cavernosa and one corpus spongiosum

Pseudodiphallia was added as a fourth category later, in which there is rudimentary atrophic penis independent from the normal penis anatomically²⁰⁴ (LOE 4)

FIGURE 8-6 Partial penile duplication.

(Photo provided courtesy of Dr. C. Ong, KK Women's and Children's Hospital, with permission.)



8.4.1.1 Materials and methods

Previously published literature in English and the available international literature were retrieved through a MEDLINE search using 5 keywords: diphallia, diphallus, bifid penis, double penis, and penile duplication. Reference lists of the searched literature were added. Predetermined criteria for inclusion consisted of focus on human male subjects; 128 articles between 1898 and 2013 were retrieved. Almost all of them were reports of one or two cases. Of the articles retrieved, 118 articles

reported the cases without exstrophy variants, and 10 articles reported the cases with rare variants of exstrophy-epispadias complex. Of these, 14 papers formed the basis for this section. These 14 papers were assessed according to the level of evidence and grade of recommendation following the ICUD Grade of Recommendation and Levels of Evidence. The papers were mostly LOE 4, which implies a grade of recommendation C at best.

8.4.2 Embryology

There is a wide variety in this anomaly, and it would not be possible to explain it by a single concept. The concept of caudal duplication syndrome was introduced to explain the diphallus with complicated anomalies such as duplication of colon-rectum-anus, lower urinary tract, spinal anomalies, and abdominal wall defect. Such anomalies originate from an abnormality of the embryonic cloaca and notochord in early gestation²⁰⁵ (LOE 4). During the development of the hindgut, the cloaca is formed that interconnects a portion of the developing digestive, urinary, and genital systems. During early gestation, mesoderm migrates caudally, separating the urogenital sinus from the rectum. Around the lateral margins of the cloacal plate, the paired columns of mesoderm are emerged, which is an anlage structure involved in the further development of the genital tubercle. If duplication of the cloacal membrane occurs, the migrating mesoderm can surround both cloacal membranes. Complete diphallus has a longitudinal duplication of the cloacal membranes to form 2 genital tubercles. The degree of separation of these cloacal membranes may produce anomalies such as anterior wall defects, bladder exstrophy, and hind gut anomalies, and may explain the anorectal anomalies included in the caudal duplication syndrome, which sometimes also includes diphallia^{198,205} (LOE 4).

Mirshemirani *et al.* reported 6 cases of diphallus; 5 were complete and 1 was bifid (incomplete; **Figure 8-7**).²⁰⁶ The authors explained diphallia as either the separation of the pubic tubercle, where each phallus will have only one corporal body and urethra, or the cleavage of the pubic tubercle, where each phallus will have 2 corporal bodies and urethra (LOE 4).

FIGURE 8-7 Penile duplication; complete corporal duplication.

(Photo provided courtesy of Dr. Rien Nijman, The Netherlands.)



Most reported cases were sporadic, and the karyotype in cases of diphallus has been found to be normal, with the exception of a case associated with a balanced reciprocal translocation 46,XY, t(1;14) (p36.3;q24.3)^{207,208} (LOE 4).

8.4.3 **Presentation**

In almost all cases the diagnosis of diphallia is made by its typical appearance.

- Diphallia can be associated with:
- Double bladder and double urethra
- Single bladder and duplicated urethra
- Single bladder and single urethra

The urethra may be fully patent, stenotic, atretic, hypospadiac, epispadiac, or a blind end in each penis²⁰⁷ (LOE 4). When the urethra is fully developed in both penises, urination usually occurs simultaneously even though the bladder is single or duplicated. But many variations are possible, and full investigation with imaging (ultrasound, voiding cystourethrograph, magnetic resonance imaging) is mandatory.

In a rare case, it was reported that erection occurred from one penis, while urination occurred from the other penis independently²⁰⁹ (LOE 4).

8.4.4 Surgical treatment

In the neonatal period, treatment will be determined by acute problems caused by obstruction (like in rectal anomalies). Multiple system anomalies are common and should be addressed before the diphallia needs to be dealt with. Careful planning and counseling of the parents needs to precede the surgical correction.

Treatment of diphallia is focused on the function of urination and erection as well as cosmesis. In general, each patient is different and treatment should be individualized. The treatment can be delayed after school age or even adulthood in some cases^{209,210} (LOE 4).

The surgical options for cosmetic and functional reconstruction of diphallia are based on the position and development of the penis and the urethra, and the number of corpora cavernosa. The common management is the resection of the rudimental or less well developed penis with urethra, particularly when the 2 penises are located vertically. If penises are located transversely, joining of 2 penises can be chosen as penoplasty in both single and double corporal bodies²¹¹ (LOE 4). In adult cases, more complicated microsurgical reconstruction may be indicated (LOE 4).

During reconstruction of diphallia, the urethra may be reconstructed simultaneously or as a staged operation. If the urethra is duplicated, the functional urethra should be preserved. If the urethra is hypospadiac or epispadiac, conventional repair will be indicated. For a duplicated bladder, the standard technique is to join the 2 bladders. As long-term follow-up data on the functionality of the penis and bladder is lacking, close and long-term follow-up is mandatory.

8.4.5 **Recommendation**

Treatment of patients with diphallia is highly individualized and needs to be done solely in specialized centres.

8.5 **Penoscrotal Transposition**

8.5.1 Introduction

Penoscrotal transposition is an uncommon abnormality of male external genitalia. It may be complete or incomplete. In the complete form, the scrotum is located cephalad to the penis, which emerges from the perineum. This form is an extremely rare condition, with only dozens of cases reported to date. It is frequently associated with complicated abnormalities of other organs. The incomplete form is less severe and much more common than the complete type. It is frequently associated with hypospadias.

8.5.1.1 Materials and methods

Previously published literature in English and the available international literature were retrieved through a MEDLINE search using 5 keywords: penoscrotal transposition, scrotal transposition, prepenile scrotum, ectopic phallus, and ectopic penis. Predetermined criteria for inclusion consisted of focus on the human male subject. The search yielded 159 articles between 1911 and 2012, of which 69 articles referred to scrotal transposition with hypospadias. The others referred to scrotal transposition without hypospadias; most reported one or two cases. One article reported a large series with 53 cases, including 11 cases without hypospadias. Fifty-two articles were related to surgical procedures or outcomes. Summaries of articles were reviewed with the full text of the relevant article, and 20 articles formed the basis for this section. These papers were reviewed for level of evidence and assigned grade of recommendation according to the ICUD guidelines. Overall, the relevant papers were not evidence-based articles, but rather were descriptive studies. Hence the grade of recommendation is C at best.

8.5.2 Embryology

When the genital tubercle is normally developed, the labioscrotal swellings are anterior to the genital tubercle at 9 to 11 weeks of gestation. They then migrate infero-medially and fuse in the midline caudal to the penis by the 12th week. The embryological pathogenesis of penoscrotal transposition is still unclear, but it is suggested that an abnormal positioning of the genital tubercle in relation to the scrotal swellings during the critical 4th to 5th week of gestation could affect the migration of the labioscrotal swellings.

8.5.3 **Presentation**

Penoscrotal transposition can be easily diagnosed because of its characteristic appearance (**Figure 8-8**). In the complete form, examination of other organ systems is mandatory. If the urethra is normally developed even though hypospadiac, renal function may be preserved. However, if the urethra is atretic, renal function may be severely affected. Prenatal diagnosis can be made by ultrasonography^{212–214} (LOE 4, LOE 4, LOE 1). In the case of underdevelopment of the urethra or urethral atresia, oligohydramnios will be present, and prenatal vesicoamniotic shunting could be indicated to preserve renal and respiratory function.

FIGURE 8-8 Penoscrotal transposition; complete transposition.

(Photo provided courtesy of Dr. A Jacobsen, KK Women's and Children's Hospital.)



8.5.4 **Associated anomalies**

The incomplete form of penoscrotal transposition is very often associated with hypospadias^{215–217} (LOE 4), particularly with the proximal type, and bifid scrotum.

The complete form is mostly associated with major malformations such as cardiac anomalies, gastrointestinal abnormalities including rectal atresia, craniofacial anomalies, renal and genitourinary anomalies, and malformations of the musculoskeletal system or central nervous system. Some of these anomalies can be life threatening. It may represent a part of a wide spectrum of anomalies resulting from a major embryological insult during early gestation. The complete form may be part of one of the various malformations in the vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities (VACTERL) association, distal 13q deletion syndrome^{218–220} (LOE 4), or presence of mosaic trisomy 18²²¹ (LOE 4). In these groups, the clinical outcome is serious and sometimes fatal. Al-Zaiem reported a case of caudal regression syndrome with penoscrotal transposition and observed that 38% of reported penoscrotal transposition showed an association with caudal regression syndrome²²² (LOE 4).

8.5.5 Surgical treatment

Different surgical techniques have been described. For the incomplete form, the apex of the upper scrotal flaps are mobilized and brought down to the ventral root of the penis as Glenn-Anderson's technique or its modification^{215,216,223-226} (LOE 4, LOE 2). One-stage repair can be done with hypospadias repair in many cases. In cases with severe proximal hypospadias, it can be reconstructed after scrotoplasty²²⁷⁻²²⁹ (LOE 4). For the complete form, the surgery is more challenging and the choice of treatment should be focused on the life-threatening problems of other organ systems. In the complete type, repair with local skin manoeuvres may be inadequate, and a staged repair is recommended. The deep mobilization of the penile shaft is necessary to bring the penis in a more cephalad position. Sometimes it is also necessary to detach the corporal bodies in order to realign the penis^{230,231} (LOE 5). Hypospadias repair is the final step if associated.

8.5.6 **Recommendations**

Penoscrotal transposition is usually associated with proximal hypospadias and may be corrected during hypospadias correction or as a second stage procedure.

The complete type of transposition is rare and is usually part of complex congenital malformations. Treatment is always secondary to correction of the other anomalies, and should only be done in centres with expertise.

8.6 Aphallia

8.6.1 Introduction

Aphallia is an extremely rare condition and the literature is descriptive and retrospective. In 1997, Hendren reported on 5 cases and quoted an incidence of 1 in 30 million births²³² (LOE 4). Other authors have quoted an estimated incidence of 1 in 10–30 million²³³ (LOE 4; **Figure 8-9**).

A complete workup of the child is recommended at birth, as multiple anomalies may co-exist^{234,235} (LOE 4). A patient with cloacal exstrophy may be thought to be aphalli, but the phallies in some cases have been reported as intra-vesical^{236,237} (LOE 4).

The only attempt at classification of aphallia was published in 1989, based on 3 cases and a literature review of 50 applicable case reports²³⁸ (LOE 4). The proposed classification is related to prognosis and has not been in use subsequently. The authors postulate that the relative relationship of the urethral meatus to the anal sphincter will determine the prognosis, with the post-sphincteric patients having highest survival and lowest incidence of other abnormalities.

8.6.1.1 Materials and methods

A literature search using the keyword aphallia yielded 44 hits; of those, 40 articles were reviewed. Eight articles included a variety of other causes for a small penis as well as feminizing genitoplasty, and were descriptive papers of surgical techniques used for phalloplasty. Twenty-four papers are case reports, the majority with single cases, four with 3 cases, one with 4 cases, and one with 5 cases. The studies were assessed according to the level of evidence and grade of recommendation. The majority of papers for this rare condition were not evidence based.

8.6.2 **Rearing**

Earlier reports all favour female sex for rearing and a feminizing genitoplasty^{232,238} (LOE 4). However, several papers have questioned this practice, noting that patients with normal androgen levels, as in genetic males, should be reared male as they have male gender identity²³⁹ (LOE 2). In fact patients who present late and are reconstructed after puberty are satisfied following phalloplasty²⁴⁰ (LOE 4).

FIGURE 8-9 Aphallia. (Photo provided courtesy of Dr. Rien Nijman, The Netherlands.)



8.6.3 **Timing of surgery**

In the published literature (case reports), many patients are reconstructed after puberty simply because this was the time of presentation²⁴¹ (LOE 4). If the child presents earlier, other associated malformations will decide and impact the timing of genital reconstruction (this is based on common sense and not on any evidence).

8.6.5 **Phalloplasty**

The most recent phalloplasty techniques use a radial forearm free flap²⁴² (LOE 4). Local/lower abdominal wall flaps are also described with success²⁴³ (LOE 4). The phalloplasty techniques are often staged and temporizing surgery is described in childhood^{244,245} (LOE 4).

Pedicled skin flap combined with buccal mucosa graft urethroplasty has also been described with satisfactory results (3 cases)²⁴⁰ (LOE 4). Physicians should consider donor site morbidity, complexity of surgery, and recovery time when planning for surgery. A sensate neo-phallus and the option of future placement of a penile prosthesis should also be considered²⁴⁶ (LOE 2).

8.6.6 **Recommendations**

Published literature based on high level of evidence does not exist, as aphallia is an extremely rare condition. Surgical treatment is staged and should be carried out in a centre with relevant expertise.



8.7 **References**

- Barthold JS. Abnormalities of the testis and scrotum and their surgical management, in Wein MD (Ed): Campbell-Walsh Urology 10th ed. Philadelphia, Elsevier Saunders, 2012, vol 4, pp 3557–3596.
- Gres' AA, and Shmygira MB. (Urologic diseases in boys and adolescents found during targeted prophylactic examinations) [Article in Russian]. Urol Nefrol (Mosk). 1992;(4-6):40-42.
- 3. Belloli G, D'Agostino S, Pesce C, *et al.* (Varicocele in childhood and adolescence and other testicular anomalies: an epidemiological study) [Article in Italian]. Pediatr Med Chir. 1993;15(2):159-62.
- 4. Pfeiffer D, Berger J, Schoop C, *et al.* A Doppler-based study on the prevalence of varicocele in German children and adolescents. Andrologia. 2006;38(1):13-9.
- 5. Audry G, Tazi M, Bruezière J. (Varicocele in the child and adolescent) [Article in French]. Ann Urol (Paris). 1986;20(5):355-359.
- Akbay E, Cayan S, Doruk E, et al. The prevalence of varicocele and varicocele-related testicular atrophy in Turkish children and adolescents. BJU Int. 2000;86(4):490-493.
- Zivkovic D, Varga J, Grebeldinger S, et al. (External genital abnormalities in male schoolchildren: an epidemiological study) [Article in Serbian]. Med Pregl. 2004; 57(5-6):275-278.
- 8. Risser WL, and Lipshultz LI. Frequency of varicocele in black adolescents. J Adolesc Health Care. 1984;5(1):28-29.
- 9. Cervellione RM, Corroppolo M, and Bianchi A. Subclinical varicocele in the pediatric age group. J Urol. 2008;179(2):717-719.
- Keene DJ, Sajad Y, Rakoczy G, *et al.* Testicular volume and semen parameters in patients aged 12 to 17 years with idiopathic varicocele. J Pediatr Surg. 2012;47(2):383-385.
- Jones MA, Sharp GH, and Trainer TD. The adolescent varicocele. A histopathologic study of 13 testicular biopsies. Am J Clin Pathol. 1988;89(3):321-328.
- 12. Akzhigitov GN, Strakhov SN, Bondarenko SG, *et al.* (Venous drainage of the testis and the causes of the development of varicocele in children) [Article in Russian]. Khirurgiia (Mosk). 1990; 8:67-70.
- Karadeniz-Bilgili MY, Basar H, Simsir I, et al. Assessment of sapheno-femoral junction continence in patients with primary adolescent varicocoele. Pediatr Radiol. 2003;33(9):603-606.
- Severgina ES, Leonova IV, Konovalov DM, et al. (Variants of formation of v. testicularts sinistra in children with varicocele) [Article in Russian]. Arkh Patol. 2006;68(1):33-35.
- 15. Gat Y, Zukerman ZV, Bachar GN, et al. Adolescent varicocele: is it a unilateral disease? Urology. 2003;62(4):742-747.
- Chen JJ, Ahn HJ, Junewick J, et al. Is the comparison of a left varicocele testis to its contralateral normal testis sufficient in determining its well-being? Urology. 2011;78(5):1167-1172.
- Van Batavia JP. Adolescent varicocele: influence of Tanner stage at presentation on the presence, development, worsening and/ or improvement of testicular hypotrophy without surgical intervention. J Urol. 2010;184(4 Suppl):1727-1732.
- 18. Stavropoulos NE, Mihailidis I, Hastazeris K, et al. Varicocele in schoolboys. Arch Androl. 2002;48(3):187-192.
- 19. Baek, M, Park SW, Moon KH, *et al.* Nationwide survey to evaluate the prevalence of varicoceles in South Koreanmiddle school boys: a population based study. Int J Urol. 2011;18(1):55-60.
- 20. Delaney DP, Carr MC, Kolon TF, et al. The physical characteristics of young males with varicocoele. BJU Int. 2004;94(4):624-626.
- 21. Prabakaran S, Kumanov P, Tomova A, et al. Adolescent varicocele: association with somatometric parameters. Urol Int. 2006;77(2):114-117.
- Yigitler C, Yanardag H, Silit E, et al. Evaluation of inguinoscrotal pathologies among adolescents with special emphasis on association between varicocele and body mass index. Urol J. 2012;9(3):592-599.
- 23. Kumanov P, Robeva RN, and Tomova A. Adolescent varicocele: who is at risk? Pediatrics. 2008;121(1):e53-57.
- 24. Zampieri N, and Dall'Agnola A. Subclinical varicocele and sports: a longitudinal study. Urology. 2011;77(5):1199-1202.

- 25. Rigano E, Santoro G, Impellizzeri P, *et al.* Varicocele and sport in the adolescent age. Preliminary report on the effects of physical training. J Endocrinol Invest. 2004;27(2):130-132.
- 26. Mohammadali Beigi F, Mehrabi S, et al. Varicocele in brothers of patients with varicocele. Urol J., 2007;4(1):33-35.
- 27. Yagil Y, Naroditsky I, Milhem J, *et al.* Role of Doppler ultrasonography in the triage of acute scrotum in the emergency department. J Ultrasound Med. 2010;29(1):11-21.
- Rizvi SA, Ahmad I, Siddiqui MA, et al. Role of color Doppler ultrasonography in evaluation of scrotal swellings: pattern of disease in 120 patients with review of literature. Urol J. 2011;8(1):60-65.
- Kim TB, Chang JH, Yoon SJ, et al. Hydrodynamic relationship between color Doppler ultrasonography findings and the number of internal spermatic veins in varicoceles. Yonsei Med J. 2012;53(2):386-392
- Cimador M, Di Pace MR, Peritore M, et al. The role of Doppler ultrasonography in determining the proper surgical approach to the management of varicocele in children and adolescents. BJU Int. 2006;97(6):1291-1297
- 31. Walker AR, and Kogan BA. Cost-benefit analysis of scrotal ultrasound in treatment of adolescents with varicocele. J Urol. 2010;183(5):2008-2011.
- Diamond DA, Paltiel HJ, DiCanzio J, et al. Comparative assessment of pediatric testicular volume: orchidometer versus ultrasound. J Urol. 2000;164(3 Pt 2):1111-1114.
- Pilatz A, Altinkilic B, Köhler E, et al. Color Doppler ultrasound imaging in varicoceles: is the venous diameter sufficient for predicting clinical and subclinical varicocele? World J Urol. 2011;29(5):645-650.
- Kulis T, Kolaric D, Karlovic K, et al. Scrotal infrared digital thermography in assessment of varicocele--pilot study to assess diagnostic criteria. Andrologia. 2012;44 Suppl 1:780-785.
- Zampieri N, Zuin V, Corroppolo M, et al. Relationship between varicocele grade, vein reflux and testicular growth arrest. Pediatr Surg Int. 2008;24(6):727-730.
- Waalkes R, Manea IF, and Nijman JM. Varicocele in adolescents: a review and guideline for the daily practice. Arch Esp Urol. 2012;65(10):859-871.
- 37. Batavia JP, Badalato G, Fast A, *et al.* Adolescent Varicocele: Is the 20/38 Harbinger a Durable Predictor of Testicular Asymmetry? J Urol. 2012;189(5):1897-901.
- 38. Chen LK, and Chen SS. Risk factors for developing pain in normospermic patients with varicocoele. Int J Androl. 2012;35(2):176-180
- 39. Maclachlan LS, Nees SN, Fast AM, et al. Intratesticular varicoceles: Are they significant? J Pediatr Urol. 2013. ;9(6 Pt A):851-855.
- 40. de la Peña Zarzuelo E, Caffaratti Sfulcini J, and Garat Barredo JM. (The treatment of varicocele in adolescents) [Article in Spanish]. Arch Esp Urol. 2004;57(9):995-1002.
- 41. Bolla G, Sartore G, and Cumba D. (Early surgical therapy for idiopathic varicocele) [Article in Italian]. Pediatr Med Chir. 2007;29(6):340-342.
- 42. Kraeft H, Kriz-Klimek H, and Holschneider AM. (Experience with surgery for varicocele in childhood (author's transl)) [Article in German]. Z Kinderchir. 1981;34(3):272-274.
- 43. Okuyama A, Nakamura M, Namiki M, *et al.* Surgical repair of varicocele at puberty: preventive treatment for fertility improvement. J Urol.1988;139(3):562-564.
- 44. Kass EJ, and Marcol B. Results of varicocele surgery in adolescents: a comparison of techniques. J Urol. 1992;148(2 Pt 2):694-696.
- 45. Kondakov VT, Okulov AB, Tandilava RZ, *et al.* (Modified technique of the Ivanissevich operation for varicocele in children) [Article in Russian]. Klin Khir. 1992;(6):9-12.
- 46. Lucas AP, and Santos AS. (Pediatric varicocele) [Article in Portuguese]. Acta Med Port. 1998;11(7):623-626.
- Tsikopoulos GK, Roussis XS, Georgakis J, et al. Does incision of the tunica vaginalis during the Palomo procedure prevent postoperative hydrocele? Br J Urol. 1998;81(4):612-613.
- Cimador M, Castagnetti M, Ajovalasit V, et al. Sub-inguinal interruption of dilated veins in adolescent varicocele: should it be considered a gold standard technique Minerva Pediatr. 2003;55(6):599-605.

- 49. Cayan S, Acar D, Ulger S, *et al.* Adolescent varicocele repair: long-term results and comparison of surgical techniques according to optical magnification use in 100 cases at a single university hospital. J Urol. 2005;174(5):2003-7.
- Schiff J, Kelly C, Goldstein M, et al. Managing varicoceles in children: results with microsurgical varicocelectomy. BJU Int. 2005;95(3):399-402.
- Minevich E, Wacksman J, Lewis AG, et al. Inguinal microsurgical varicocelectomy in the adolescent: technique and preliminary results. J Urol. 1998;159(3):1022-1024.
- Kocvara R, Sedlácek J, Dolezal J, et al. (Microsurgical subinguinal varicocelectomy in children and adolescents) [Article in Czech]. Cas Lek Cesk. 2007;146(10):763-766.
- Kondoh N, Kun K, Ueda Y, et al. (Results of microsurgical varicocelectomy in the adolescent) [Article in Japanese]. Nihon Hinyokika Gakkai Zasshi, 2009;100(4):519-524.
- Yaman O, Soygur T, Zumrutbas AE, et al. Results of microsurgical subinguinal varicocelectomy in children and adolescents. Urology. 2006;68(2):410-412.
- Sinanoglu O, Eyyupoglu SE, and Ekici S. Ipsilateral testicular catch-up growth rate following microsurgical inguinal adolescent varicocelectomy. Scientific World Journal. 2012;2012:356374.
- Spinelli C1, Di Giacomo M, Lo Piccolo R, et al. The role of testicular volume in adolescents with varicocele: the better way and time of surgical treatment. J Urol. 2010;184(4 Suppl):1722-1726.
- Wong J, Chan S, Pagala M, et al. Lymphatic sparing microscopic retroperitoneal varicocelectomy: a preliminary experience. J Urol. 2009;182(5):2460-2463.
- Schwentner C, Oswald J, Lunacek A, et al. Optimizing the outcome of microsurgical subinguinal varicocelectomy using isosulfan blue: a prospective randomized trial. J Urol. 2006;175(3 Pt 1):1049-1052.
- Camoglio FS. Microsurgical spermatico-epigastric venous anastomosis in the treatment of varicocele in children: assessment of long-term patency. Eur J Pediatr Surg. 2003;13(4):256-259.
- Lima M, Dòmini M, and Libri M. The varicocele in pediatric age: 207 cases treated with microsurgical technique. Eur J Pediatr Surg. 1997;7(1):30-33.
- Feber KM, and Kass EJ. Varicocelectomy in adolescent boys: long-term experience with the Palomo procedure. J Urol. 2008;180(4 Suppl):1657-1659.
- 62. Niedzielski J, and Paduch DA. Recurrence of varicocele after high retroperitoneal repair: implications of intraoperative venography. J Urol. 2001;165(3):937-940.
- 63. Hart RR, Rushton HG, and Belman AB. Intraoperative spermatic venography during varicocele surgery in adolescents. J Urol. 1992;148(5):1514-1516.
- 64. Gorenstein A, Katz S, and Schiller M. Surgical treatment of varicocele in children. Isr J Med Sci. 1988;24(3):172-174.
- 65. Campobasso P. Blue venography in adolescent varicocelectomy: a modified surgical approach. J Pediatr Surg. 1997;32(9):1298-1301.
- Rais-Bahrami S, Montag S, George AK, et al. Angiographic findings of primary versus salvage varicoceles treated with selective gonadal vein embolization: an explanation for surgical treatment failure. J Endourol. 2012;26(5):556-560.
- Sivanathan C, and Abernethy LJ. Retrograde embolisation of varicocele in the paediatric age group: a review of 10 years' practice. Ann R Coll Surg Engl. 2003;85(1):50-51.
- Pedrerol A, Blanco JA, Sampere J, et al. (Venous embolization--treatment of choice in varicoceles) [Article in Spanish]. Cir Pediatr. 2011;24(1):55-58.
- Fayad F, Sellier N, Chabaud M, et al. Percutaneous retrograde endovascular occlusion for pediatric varicocele. J Pediatr Surg. 2011;46(3):525-529.
- Hawkins CM, Racadio JM, McKinney DN et al. Varicocele retrograde embolization with boiling contrast medium and gelatin sponges in adolescent subjects: a clinically effective therapeutic alternative. J Vasc Interv Radiol. 2012;23(2):206-210.
- Piñera JG, Fernández-Córdoba MS, Anselmi EH, et al. (Results of the percutaneous retrograde embolization as the first choice in the treatment of varicocele) [Article in Spanish]. Cir Pediatr. 2009;22(3):128-133.

- 72. Rivilla F, and Casillas JG. Testicular size following embolization therapy for paediatric left varicocele. Scand J Urol Nephrol. 1997;31(1):63-65.
- 73. Calama Santiago JA, Penedo Cobos JM, Molina López MY, *et al.* (Paediatric varicocele embolization dosimetric study) [Article in Spanish]. Actas Urol Esp. 2008;32(8):833-842.
- 74. Ayechu-Díaz A, Oscoz-Lizarbe M, Pérez-Martínez A, *et al.* (Treatment of adolescent varicocele: is percutaneous embolization better?) [Article in Spanish]. Cir Pediatr. 2009;22(3):134-138.
- 75. Zaupa P, Mayr J, and Höllwarth ME. Antegrade scrotal sclerotherapy for treating primary varicocele in children. BJU Int. 2006;97(4):809-812.
- Ficarra V, Sarti A, Novara G, et al. Modified antegrade scrotal sclerotherapy in adolescent patients with varicocele. J Pediatr Surg. 2004;39(7):1034-1036.
- 77. Granata C, Oddone M, Toma P, *et al.* Retrograde percutaneous sclerotherapy of left idiopathic varicocele in children: results and follow-up. Pediatr Surg Int. 2008;24(5):583-587.
- Fette A, and Mayr J. Treatment of varicoceles in childhood and adolescence with Tauber's antegrade scrotal sclerotherapy. J Pediatr Surg. 2000;35(8):1222-1225.
- Thon WF, Gall H, Danz B, et al. Percutaneous sclerotherapy of idiopathic varicocele in childhood: a preliminary report. J Urol. 1989;141(4):913-915.
- 80. Lopez C, Serres-Cousine O, and Averous M. (Varicocele in adolescents. Treatment by sclerotherapy and percutaneous embolization: reflections on the method. Apropos of 23 cases) [Article in French]. Prog Urol. 1998;8(3):382-387.
- Reiner E, Pollak JS, Henderson KJ, et al. Initial experience with 3% sodium tetradecyl sulfate foam and fibered coils for management of adolescent varicocele. J Vasc Interv Radiol. 2008;19(2 Pt 1):207-210.
- Pieri S, Agresti P, Morucci M, et al. (A transbranchial approach for the percutaneous therapy of pediatric varicocele) [Article in English, Italian]. Radiol Med. 2003;106(3):221-231.
- 83. Mazzoni G, Fiocca G, Minucci S, *et al.* Varicocele: a multidisciplinary approach in children and adolescents. J Urol. 1999;162(5):1755-1758.
- 84. Storm DW, Hogan MJ, Jayanthi VR, et al. Initial experience with percutaneous selective embolization: A truly minimally invasive treatment of the adolescent varicocele with no risk of hydrocele development. J Pediatr Urol. 2010;6(6):567-571
- Alqahtani A, Yazbeck S, Dubois J, et al. Percutaneous embolization of varicocele in children: A Canadian experience. J Pediatr Surg. 2002;37(5):783-785.
- Lebed B, Packer M, Husmann D, et al. Results and complications of adolescent varicocele repair with intraoperative sodium morrhuate sclerotherapy. J Urol. 2008;180(4 Suppl):1837-1841.
- Carmignani L, Casellato S, Galasso G, et al. Sclerotherapy of the pampiniform plexus with modified Marmar technique in children and adolescents. Urol Int. 2009;82(2):187-190.
- Cohen Z, Yulevich A, Kapuler V, et al. (Laparoscopic spermatic vein ligation: first experience in the treatment for varicocele in adolescents) [Article in Hebrew]. Harefuah. 1999;136(8):602-4, 659.
- 89. Urbanowicz W, and Górniak M. (Laparoscopic treatment of varicocele in boys) [Article in Polish]. Wiad Lek. 1998;51 Suppl 3:25-28.
- Belloli G, Musi L, and D'Agostino S. Laparoscopic surgery for adolescent varicocele: preliminary report on 80 patients. J Pediatr Surg. 1996;31(11):1488-1490.
- Keys C, Barbour L, O'Toole S, et al. Laparoscopic surgery for varicoceles in children: an audit in a single centre. J Laparoendosc Adv Surg Tech A. 2009;19 Suppl 1:S107-109.
- Méndez-Gallart R, Bautista Casasnovas A, Estévez Martínez E, et al. Reactive hydrocele after laparoscopic Palomo varicocele ligation in pediatrics [Article in English, Spanish]. Arch Esp Urol. 2010;63(7):532-536.
- Méndez-Gallart R, Bautista Casasnovas A, Estévez-Martínez E, et al. Laparoscopic Palomo varicocele surgery: lessons learned after 10 years' follow up of 156 consecutive pediatric patients. J Pediatr Urol. 2009;5(2):126-131.
- Barqawi A, Furness P 3rd, and Koyle M. Laparoscopic Palomo varicocelectomy in the adolescent is safe after previous ipsilateral inguinal surgery. BJU Int. 2002;89(3):269-272.

- Hassan JM, Adams MC, Pope JC 4th, et al. Hydrocele formation following laparoscopic varicocelectomy. J Urol. 2006;175(3 Pt 1):1076-1079.
- 96. Zhila VV, Shodmonova ZR, Rublevskii VP, et al. (High resection of the left testicular vein and ligation of the internal iliac artery using a retroperitoneoscope) [Article in Russian]. Klin Khir. 1991;(5):49-51.
- Cobellis G, Mastroianni L, Cruccetti A, et al. Retroperitoneoscopic varicocelectomy in children and adolescents. J Pediatr Surg. 2005;40(5):846-849.
- Sun N, Cheung TT, Khong PL, et al. Varicocele: Laparoscopic clipping and color Doppler follow-up. J Pediatr Surg. 2001;36(11):1704-1707.
- Huk J, Fryczkowski M, Kaletka Z, et al. (Comparison of testicular volume before and after laparoscopic varicocelectomy in children and adolescents) [Article in Polish]. Med Wieku Rozwoj. 2006;10(3 Pt 2):885-891.
- 100. Humphrey GM, and Najmaldin AS. Laparoscopy in the management of pediatric varicoceles. J Pediatr Surg. 1997;32(10):1470-1472.
- Cohen RC. Laparoscopic varicocelectomy with preservation of the testicular artery in adolescents. J Pediatr Surg. 2001;36(2):394-396.
- Poddoubnyĭ IV, Dronov AF, Kovarskiĭ SL, et al. Laparoscopic ligation of testicular veins for varicocele in children. A report of 180 cases. Surg Endosc. 2000;14(12):1107-1109.
- Varlet F, Becmeur F, and Groupe d'Etudes en Coeliochirurgie Infantile. Laparoscopic treatment of varicoceles in children. Multicentric prospective study of 90 cases. Eur J Pediatr Surg. 2001;11(6):399-403.
- Esposito C, Monguzzi GL, Gonzalez-Sabin MA, et al. Laparoscopic treatment of pediatric varicocele: a multicenter study of the italian society of video surgery in infancy. J Urol. 2000;163(6):1944-1946.
- Zampieri N, Zuin V, Corroppolo M, et al. Varicocele and adolescents: semen quality after 2 different laparoscopic procedures. J Androl. 2007;28(5):727-733.
- 106. Cimador M, Di Pace MR, Sergio M, et al. Laparoscopic surgery of deferential reflux in pediatric and adolescent varicocele. J Laparoendosc Adv Surg Tech A. 2009;19 Suppl 1:S133-136.
- Nyirády P, Kiss A, Pirót L, et al. Evaluation of 100 laparoscopic varicocele operations with preservation of testicular artery and ligation of collateral vein in children and adolescents. Eur Urol. 2002;42(6):594-597.
- Nyirády P, Pirót L, Altorjay A, et al. Laparoscopic varicocele operation: a chance to prevent the recurrence. Acta Chir Hung. 1998;37(3-4):201-204.
- Koyle MA, Oottamasathien S, Barqawi A, et al. Laparoscopic Palomo varicocele ligation in children and adolescents: results of 103 cases. J Urol. 2004;172(4 Pt 2):1749-52.
- Marte A, Sabatino MD, Borrelli M, et al. LigaSure vessel sealing system in laparoscopic Palomo varicocele ligation in children and adolescents. J Laparoendosc Adv Surg Tech A. 2007;17(2):272-275.
- 111. Sasagawa I, Yazawa H, Suzuki Y, *et al.* Laparoscopic varicocelectomy in adolescents using an ultrasonically activated scalpel. Arch Androl. 2000;45(2):91-94.
- Polok M, Patkowski D, Apoznański W, et al. Electrocoagulation versus clips in laparoscopic varicocelectomy in boys. J Laparoendosc Adv Surg Tech A. 2010;20(3):277-280.
- Liang Z, Guo J, Zhang H, et al. Lymphatic sparing versus lymphatic non-sparing laparoscopic varicocelectomy in children and adolescents: a systematic review and meta-analysis. Eur J Pediatr Surg. 2011;21(3):147-153.
- 114. Kocvara R, Dvorácek J, Sedlácek J, *et al.* Lymphatic sparing laparoscopic varicocelectomy: a microsurgical repair. J Urol. 2005;173(5):1751-1754.
- Healey C, Lisle R, and Mahomed A. Outcome of lymphatic- and artery-sparing surgery for pediatric varicocoele. J Laparoendosc Adv Surg Tech A. 2010;20(4):387-389.
- Husár M, Zerhau P, Tůma J, et al. (Laparoscopic surgery varicocele in the childhood and adolescent--our experience with 202 patients) [Article in Czech]. Rozhl Chir. 2006;85(10):498-500.
- Chiarenza SF, D'Agostino S, Scarpa M, et al. Lymphography prior to laparoscopic Palomo varicocelectomy to prevent postoperative hydrocele. J Laparoendosc Adv Surg Tech A. 2006;16(4):394-396.

- 118. Schwentner C, Radmayr C, Lunacek A, *et al.* Laparoscopic varicocele ligation in children and adolescents using isosulphan blue: a prospective randomized trial. BJU Int. 2006;98(4):861-865.
- 119. Golebiewski A, Krolak M, Komasara L, *et al.* Dye-assisted lymph vessels sparing laparoscopic varicocelectomy. J Laparoendosc Adv Surg Tech A. 2007;17(3):360-363.
- 120. Glassberg KI, Poon SA, Gjertson CK, *et al.* Laparoscopic lymphatic sparing varicocelectomy in adolescents. J Urol. 2008;180(1):326-330.
- 121. Tong Q, Zheng L, Tang S, *et al.* Lymphatic sparing laparoscopic Palomo varicocelectomy for varicoceles in children: intermediate results. J Pediatr Surg. 2009;44(8):1509-1513.
- 122. Oswald J, Körner I, and Riccabona M. The use of isosulphan blue to identify lymphatic vessels in high retroperitoneal ligation of adolescent varicocele--avoiding postoperative hydrocele. BJU Int. 2001;87(6):502-504.
- 123. D'Alessio A, Piro E, Beretta F, *et al.* Lymphatic preservation using methylene blue dye during varicocele surgery: a single-center retrospective study. J Pediatr Urol. 2008;4(2):138-140.
- 124. Xie WL, Huang J, Han JL, *et al.* (Needle laparoscopic varicocelectomy) [Article in Chinese]. Zhonghua Nan Ke Xue. 2005;11(11):813-814.
- 125. Link BA, Kruska JD, Wong C, et al. Two trocar laparoscopic varicocelectomy: approach and outcomes. JSLS. 2006;10(2):151-154.
- 126. Méndez-Gallart R, Bautista Casasnovas A, Estévez-Martínez E, *et al.* Bipolar electrothermal vessel sealing system and 5-mm 2 expandable trocar approach in pediatric laparoscopic varicocelectomy: a successful time-effective technical refinement. Surg Laparosc Endosc Percutan Tech. 2011;21(5):e256-259.
- 127. Barone JG, Johnson K, Sterling M, *et al.* Laparoendoscopic single-site varicocele repair in adolescents-initial experience at a single institution. J Endourol. 2011;25(10):1605-1608.
- 128. Kaouk JH, and Palmer JS. Single-port laparoscopic surgery: initial experience in children for varicocelectomy. BJU Int. 2008;102(1):97-99.
- 129. Abadía-Forcén T, Ayuso-González L, Pisón-Chacón J, *et al.* Lymphatic preservation in varicocele in the adolescent: does prior embolization limit spermatic dissection? J Pediatr Urol. 2012;8(4):431-433.
- 130. Hidalgo-Tamola J, Sorensen MD, Bice JB, *et al.* Pediatric robot-assisted laparoscopic varicocelectomy. J Endourol. 2009;23(8):1297-300.
- 131. Podkamenev VV, Stalmakhovich VN, Urkov PS, *et al.* Laparoscopic surgery for pediatric varicoceles: Randomized controlled trial. J Pediatr Surg. 2002;37(5):727-729.
- 132. Bebars GA, Zaki A, Dawood AR, *et al.* Laparoscopic versus open high ligation of the testicular veins for the treatment of varicocele. JSLS. 2000;4(3):209-213.
- 133. Barroso U Jr, Andrade DM, Novaes H, *et al.* Surgical treatment of varicocele in children with open and laparoscopic Palomo technique: a systematic review of the literature. J Urol. 2009;181(6):2724-2728.
- 134. Borruto FA, Impellizzeri P, Antonuccio P, *et al.* Laparoscopic vs open varicocelectomy in children and adolescents: review of the recent literature and meta-analysis. J Pediatr Surg. 2010;45(12):2464-2469.
- 135. Diamond DA, Xuewu J, Cilento BG Jr, *et al.* Varicocele surgery: a decade's experience at a children's hospital. BJU Int. 2009;104(2):246-249.
- 136. Riccabona M, Oswald J, Koen M, *et al.* Optimizing the operative treatment of boys with varicocele: sequential comparison of 4 techniques. J Urol. 2003;169(2):666-668.
- 137. VanderBrink BA, Palmer LS, Gitlin J, *et al.* Lymphatic-sparing laparoscopic varicocelectomy versus microscopic varicocelectomy: is there a difference? Urology. 2007;70(6):1207-1210.
- 138. Castagnetti M, Cimador M, Catalano P, et al. Evolving management of adolescent varicocele. J Pediatr Urol. 2008;4(2):107-112.
- Escala JM, Cadena Y, Valenzuela S, et al. (Varicocele in the adolescent. What is the best surgical option?) [Article in Spanish]. Arch Esp Urol. 2008;61(6):691-694.
- 140. Moreira-Pinto J, Osório AL, Carvalho F, *et al.* Varicocoelectomy in adolescents: laparoscopic versus open high ligation technique. Afr J Paediatr Surg. 2011;8(1):40-43.

- Niyogi A, Singh S, Zaman A, et al. Varicocele surgery: 10 years of experience in two pediatric surgical centers. J Laparoendosc Adv Surg Tech A. 2012;22(5):521-525.
- Cimador M, Pensabene M, Sergio M, et al. Focus on paediatric and adolescent varicocoele: a single institution experience. Int J Androl. 2012;35(5):700-705.
- Pintus C, Rodriguez Matas MJ, Manzoni C, et al. Varicocele in pediatric patients: comparative assessment of different therapeutic approaches. Urology. 2001;57(1):154-157.
- 144. Mazzoni G, Spagnoli A, Lucchetti MC, *et al.* Adolescent varicocele: Tauber antegrade sclerotherapy versus Palomo repair. J Urol. 2001;166(4):1462-1464.
- 145. Preston MA, Carnat T, Flood T, et al. Conservative management of adolescent varicoceles: a retrospective review. Urology. 2008;72(1):77-80.
- 146. Kolon TF, Clement MR, Cartwright L, et al. Transient asynchronous testicular growth in adolescent males with a varicocele. J Urol. 2008;180(3):1111-1115.
- 147. Li F, Chiba K, Yamaguchi K, *et al.* Effect of varicocelectomy on testicular volume in children and adolescents: a meta-analysis. Urology. 2012;79(6):1340-1345.
- 148. Paduch DA, and Niedzielski J. Repair versus observation in adolescent varicocele: a prospective study. J Urol. 1997;158(3 Pt 2):1128-1132.
- 149. Cayan S, Akbay E, Bozlu M, *et al.* The effect of varicocele repair on testicular volume in children and adolescents with varicocele. J Urol. 2002;168(2):731-734.
- 150. Messina M, Zagordo L, Di Maggio G, *et al.* Testicular hypotrophy in varicocele: pre and postoperative echographic follow-up in the pediatric age. Minerva Urol Nefrol. 2006;58(3):151-155.
- Zampieri N, Mantovani A, Ottolenghi A, et al. Testicular catch-up growth after varicocelectomy: does surgical technique make a difference? Urology. 2009;73(2):289-292.
- 152. Lund L, Tang YC, Roebuck D, et al. Testicular catch-up growth after varicocele correction in adolescents. Pediatr Surg Int. 1999;15(3-4):234-237.
- 153. Poon SA, Kozakowski KA, Decastro GJ, et al. Adolescent varicocelectomy: postoperative catch-up growth is not secondary to lymphatic ligation. J Pediatr Urol. 2009;5(1):37-41.
- 154. Gershbein AB, Horowitz M, and Glassberg KI. The adolescent varicocele I: left testicular hypertrophy following varicocelectomy. J Urol. 1999;162(4):1447-1449.
- 155. Woldu SL, Van Batavia JP, et al. Is adolescent varicocelectomy safe after previous inguinal surgery? J Urol. 2010;184(4 Suppl):1716-1721.
- 156. Lund L, Roebuck DJ, Lee KH, et al. Clinical assessment after varicocelectomy. Scand J Urol Nephrol. 2000;34(2):119-122.
- 157. Esposito C, Valla JS, Najmaldin A, *et al.* Incidence and management of hydrocele following varicocele surgery in children. J Urol. 2004;171(3):1271-1273.
- 158. Misseri R, Gershbein AB, Horowitz M, *et al.* The adolescent varicocele. II: the incidence of hydrocele and delayed recurrent varicocele after varicocelectomy in a long-term follow-up. BJU Int. 2001;87(6):494-498.
- 159. Nees SN, and Glassberg KI. Observations on hydroceles following adolescent varicocelectomy. J Urol. 2011;186(6):2402-2407.
- Castagnetti M, Cimador M, DiPace MR, et al. 'Preemptive hydrocelectomy' in subinguinal varicocelectomy. Urol Int. 2008;81(1):14-16.
- 161. Chrouser K, Vandersteen D, Crocker J, et al. Nerve injury after laparoscopic varicocelectomy. J Urol. 2004;172(2):691-3.
- 162. Muensterer OJ. Genitofemoral nerve injury after laparoscopic varicocelectomy in adolescents. J Urol. 2008;180(5):2155-2158.
- 163. Glassberg KI, Badalato GM, Poon SA, *et al.* Evaluation and management of the persistent/recurrent varicocele. Urology. 2011;77(5):1194-1198.
- Mohseni MJ, Nazari H, Amini E, et al. Shunt-type and stop-type varicocele in adolescents: prognostic value of these two different hemodynamic patterns. Fertil Steril. 2011;96(5):1091-1096.

- 165. Fisch H, Hyun G, and Hensle TW. Testicular growth and gonadotrophin response associated with varicocele repair in adolescent males. BJU Int. 2003;91(1):75-78.
- 166. Hienz HA, Voggenthaler J, and Weissbach L. Histological findings in testes with varicocele during childhood and their therapeutic consequences. Eur J Pediatr. 1980;133(2):139-146.
- 167. Hösli PO. (Varicocele--results following early treatment of children and adolescents) [Article in German]. Z Kinderchir. 1988;43(3):213-215.
- 168. Pozza D, Gregori A, Ossanna P, *et al.* Is it useful to operate on adolescent patients affected by left varicocele? J Androl. 1994;15 Suppl:43S-46S.
- 169. Lenzi A, Gandini L, Bagolan P, et al. Sperm parameters after early left varicocele treatment. Fertil Steril. 1998;69(2):347-349.
- D'Agostino S, Musi L, Colombo B, et al. (Varicocele: epidemiologic study and indications for its treatment) [Article in Italian]. Pediatr Med Chir. 1996;18(5 Suppl):27-30.
- 171. Armagan A, Dogan F, Oksay T, *et al.* The effect of micronized purified flavonoid fraction on the prevention of testicular pathologies in adolescent rats with experimentally induced varicocele. J Urol. 2012;188(5):2007-2013.
- 172. Zampieri N, Pellegrino M, Ottolenghi A, *et al.* Effects of bioflavonoids in the management of subclinical varicocele. Pediatr Surg Int. 2010;26(5):505-508.
- 173. Aaronson IA. Micropenis; medical and surgical implications. J Urol. 1994;152:4-14.
- 174. Lee PA, Mazur T, Danish R, et al. Micropenis. I. Criteria, etiologies and classification. Johns Hopkins Med J. 1980;146(4):156-163.
- 175. Feldman KW, and Smith DW. Fetal phallic growth and penile standards for newborn male infants. J Pediatr. 1975;86:395-398.
- 176. Schonfeld WA, and Beebe GW. Normal growth and variation in male genitalia from birth to maturity. J Urol. 1942;48:759.
- 177. Calikoglu AS. Should boys with micropenis be reared as girls? J Pediatr. 1999;134:537-538.
- 178. Husmann DA. The androgen insensitive micropenis: long-term follow-up into adulthood. J Pediatr Endocrinol Metab. 2004;17:1037-1041.
- 179. Danish RK, Lee PA, Mazur T, et al. Micropenis. II. Hypogonadotropic hypogonadism. Johns Hopkins Med J. 1980;146(5):177-84.
- Burstein S, Grumbach MM, and Kaplan SL. Early determination of androgen-responsiveness is important in the management of microphallus. Lancet. 1979;2:983-986.
- Bin-Abbas B, Conte FA, Grumbach MM, et al. Congenital hypogonadotrophic hypogonadism and micropenis: effect of testosterone treatment on adult penile size. Why sex reversal is not indicated. J Pediatr. 1999;134:579-583.
- 182. Klugo RC, and Cerny JC. Response of micropenis to topical testosterone and gonadotropin. J Urol. 1978;119(5):667-668.
- Choi SK, Han SW, Kim DH, et al. Transdermal dihydrotestosterone therapy and its effects on patients with microphallus. J Urol. 1993;150:657-660.
- 184. Srinivasan AK, Palmer LS, and Palmer JS. Inconspicuous penis. ScientificWorldJournal. 2011;11:2559-2564.
- 185. Casale AJ, Beck SD, Cain MP, et al. Concealed penis in childhood: a spectrum of etiology and treatment. J Urol. 1999;162(3):1165-1168.
- 186. Maizels M, Zaontz M, and Donovan J. Surgical correction of the buried penis: description of a classification system and a technique to correct the disorder. J Urol. 1986;136(1):268–271.
- 187. Shenoy MU, Srinivasan J, Sully L, *et al.* Buried penis: surgical correction using liposuction and realignment of skin. BJU Int. 2000;86(4):527–530.
- 188. Shapiro SR. Surgical treatment of the "buried" penis. Urology. 1987;30(6):554-559.
- Palmer JS, Elder JS, and Palmer LS. The use of betamethasone to manage the trapped penis following neonatal circumcision. Urol. 2005;174(4):1577–1578.
- 190. Montag S, and Palmer LS. Abnormalities of penile curvature: Chordee and penile torsion. ScientificWorldJournal. 2011;11:1470-1478.
- 191. Fisher PC, and Park JM. Penile torsion repair using dorsal dartos flap rotation. J Urol. 2004;171:1903-1904.

- 192. Bauer R, and Kogan BA. Modern technique for penile torsion repair. J Urol. 2009;182:286-291.
- 193. Pierrot SE, and Muthurajan S. Incidence and predictive factors of isolated neonatal penile glanular torsion. J Pediatr Urol. 2007;3:495-499.
- 194. Shaeer O. Torsion of the penis in adults: Prevalence and surgical correction. J Sex Med. 2008;5:735-739.
- 195. Snow BW. Penile torsion correction by diagonal corporal placation sutures. International Braz J Urol. 2009;35:56-59.
- 196. Zhou L, Mei H, Hwang AH, et al. Penile torsion repair by suturing tunica albuginea to the pubic periosteum. J Pediatr Surg. 2006;41:E7-9.
- 197. Aldaqadossi HA, Elgamal SA, and Seif Elnasr MK. Dorsal dartos flap rotation versus suturing tunica albuginea to the pubic periosteum for correction of penile torsion: A prospective randomized study. J Pediatr Urol. 2013;9(5):643-647.
- Liu H, Che X, Wang S, et al. Multiple-stage correction of caudal duplication syndrome: a case report. J Pediatr Surg. 2009;44:2410-2413.
- 199. Azmy AF. Complete duplication of the hindgut and lower urinary tract with diphallus. J Pediatr Surg. 1990;25:647-649.
- 200. Dewan PA, Lawrence MJ, Pip A, et al. Diphallus associated with partial caudal duplication. Pediatr Surg Int. 1998;14:131-133.
- Sarin YK, Manchanda V, Sharma A, et al. Triplication of colon with diphallus and complete duplication of bladder and urethra. J Pediatr Surg. 2006;41:1924-1926.
- 202. Mirshemirani A, Roshanzamir F, Shayeghi S, *et al.* Diphallus with imperforate anus and complete duplication of rect-sigmoid colon and lower urinary tract. Iran J Pediatr. 2010;20:229-232.
- 203. Bakheet MAAM, and Rafaei M. Penile duplication and two anal openings; report of a very rare case. Iran J Pediatr. 2012;22:133-136.
- 204. Mutlu N, Baykal M, Merder E et al. Diphallus with urethral duplications. Int Urol Nephrol. 1999;31:253-255.
- 205. Hollowell Jr JG, Witherington R, Bllagas AJ, *et al.* Embryologic considerations of diphallus and associated anomalies. J Urol. 1977;117:728-731.
- 206. Mirshemirani AR, Sadeghyian N, Mohajerzadeh L, *et al.* Diphallus: report on six cases and review of the literature. Iran J Pediatr. 2010;20:353-357.
- 207. Karna P, and Kapur S. Diphallus and associated anomalies with balanced autosomal chromosomal translocation. Clin Genet. 1994;46:209-211.
- 208. Mukunda R, Bendre PS, Redkar RG, et al. Diphallus with anorectal malformation-case report. J Pedatr Surg. 2010;45:632-634.
- 209. Sahay SC, Dogra PN, and Rai PK. A rare case of adult diphallus with anorectal malformation. Indian J Urol. 2012;28:357-358.
- 210. Huang WY, Eid AE, and Cheng KX. Diphallus in an adult: microsurgical treatment-case report. J Reconstr Microsurg. 1994;10:387-391.
- Elsawy M, Pippi Salle JL, Abdulsalam M, et al. Penile duplication: is it necessary to excise one of the penises? J Pediatr Urol. 2012;8:434-436.
- 212. Emery SP, Schneck FX, Kauffman DE, *et al.* Prenatal diagnosis of lower urinary tract obstruction associated with penoscrotal transposition. Prenat Diagn. 2009;29:1089-1090.
- 213. Nakamura Y, Jennings RW, Connolly S, *et al.* Fatal diagnosis of penoscrotal transposition associated with perineal lipoma in one twin. Fetal Diagn Ther. 2010;27:164-167.
- Wang Y, Cai A, Sun J, et al. Prenatal diagnosis of penoscrotal transposition with 2- and 3-dimensional ultrasonography. J Ultrasound Med. 2011;30:1397-1401.
- 215. Kolligian ME, Franco I, and Reda EF. Correction of penoscrotal transposition: Novel approach. J Urol. 2000;164:994-997.
- 216. Pinke LA, Rathbun SR, Husmann DA, et al. Penoscrotal transposition: Review of 53 patients. J Urol. 2001;166:1865-1868.
- Sunay M, Emir L, Karabulut A, et al. Our 21-year experience with the Thiersch-Duplay technique following surgical correction of penoscrotal transposition. Urol Int. 2009;82:28-31.
- 218. Chadha R, Mann V, Sharma A, *et al.* Complete penoscrotal transposition and associated malformations. Pediatr Surg Int. 1999;15:505-507.
- 219. Walsh LE, Vance GH, and Weaver DD. Distal 13q deletion syndrome and the VACTERL association: Case report, literature review, and possible implications. Am J Med Genet. 2001;98:137-144.

- 220. Chung JL, Choi JR, Park MS, *et al.* A case of del(13)(q22) with multiple major congenital anomalies, imperforated anus and penoscrotal transposition. Yonsei Med J. 2001;42:558-562.
- 221. Cohen-Addad N, Zarafu IW, and Hanna MK. Complete penoscrotal transposition. Urology. 1985;26:149-152.
- 222. AI-Zaiem MM. Caudal regression syndrome and penoscrotal transposition. Saudi Med J. 2001;22:544-546.
- 223. Glenn JF, and Anderson EE. Surgical correction of incomplete penoscrotal transposition. J Urol. 1973;110:603-605.
- 224. Germiyanoglu C, OzkardesH, Altug U, et al. Reconstruction of penoscrotal transposition. Br J Urol. 1994;73:200-203.
- 225. Garcia RD, Marin BC, and Tomas E. Peno-Scrotal transposition. Eur J Pediatr Surg. 1995;5:222-225.
- 226. Saleh A. Correction of incomplete transposition by a modified Glenn-Anderson technique. African J Paediatr Surg. 2010;7:181-184.
- 227. Nonomura K, Koyanagi T, Imanaka K, *et al.* One-stage total repair of severe hypospadias with scrotal transposition in 18 cases. J Pediatr Surg. 1988;23:177-180.
- 228. Perovic S, and Vukadinovic V. Penoscrotal transposition with hypospadias: 1-stage repair. J Urol. 1992;148:1510-1513.
- 229. Chen SC, Yang SSD, Hsieh CH, *et al.* One-stage correction of proximal hypospadias and penoscrotal transposition. J Formos Med Assoc. 2002;101:48-51.
- 230. Fathi K, Perovic S, and Pinter A. Successful surgical correction of an extreme form of ectopic penis. J Pediatr Urol. 2010;6:426-428.
- 231. Somoza I, Palacios MG, Mendez R, *et al.* Complete penoscrotal transposition: a three-stage procedure. Indian J Urol. 2012;28:450-452.
- 232. Hendren WH. The genetic male with absent penis and urethrorectal communication: experience with 5 patients. J Urol. 1997;157(4):1469-1474.
- 233. Wang H, Guo K, Wang J, et al. Aphallia in an adult male with 46, XY karyotype. Int J Urol. 2011;18(7):540-542.
- 234. Gérard-Blanluet M, Lambert V, Khung-Savatovsky S, *et al.* Aphallia, lung agenesis and multiple defects of blastogenesis. Fetal Pediatr Pathol. 2011;30(1):22-26.
- 235. Rattan KN, Kajal P, Pathak M, et al. Aphallia: experience with 3 cases. J Pediatr Surg. 2010;45(1):E13-16.
- 236. Fox JA, Banihani O, and Schneck FX. Is it really a hamartoma? Bringing awareness to the possibility of an intravesical phallus in the aphallic 46,xy cloacal exstrophy patient. J Pediatr Urol. 2013;9(6 Pt B):1237-1238.
- 237. Arunachalam P, Pillai SB, and Sridhar DC. Classical cloacal exstrophy with intravesical phallus. J Pediatr Surg. 2012;47(7):E5-8.
- 238. Skoog SJ, and Belman AB. Aphallia: its classification and management. J Urol. 1989;141(3):589-592.
- 239. Reiner WG. Gender identity and sex-of-rearing in children with disorders of sexual differentiation. J Pediatr Endocrinol Metab. 2005;18(6):549-553.
- 240. Bhandari M, Sinha RJ, and Singh V. Urethral reconstruction in patients suffering from aphallia: a reconstructive challenge. Urol Int. 2011;87(4):475-480.
- 241. Chibber PJ, Shah HN, Jain P, *et al.* Male gender assignment in aphallia: a case report and review of the literature. Int Urol Nephrol. 2005;37(2):317-319.
- 242. Massanyi EZ, Gupta A, Goel S, *et al.* Radial forearm free flap phalloplasty for penile inadequacy in patients with exstrophy. J Urol. 2013;190(4 Suppl):1577-1582.
- 243. Bajpai M. "Bird-Wing" abdominal phalloplasty: A novel surgical technique for penile reconstruction. J Indian Assoc Pediatr Surg. 2013;18(2):49-52.
- 244. Bajpai M. Scrotal phalloplasty: A novel surgical technique for aphallia during infancy and childhood by pre-anal anterior coronal approach. J Indian Assoc Pediatr Surg. 2012;17(4):162-164.
- 245. Willihnganz-Lawson KH, Malaeb BS, and Shukla AR. De Castro technique used to create neophallus: a case of aphallia. Urology. 2012;79(5):1149-1151.
- 246. Bluebond-Langner R, and Redett RJ. Phalloplasty in complete aphallia and ambiguous genitalia. Semin Plast Surg. 2011;25(3):196-205.

Committee



Adolescent Urology

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9.1 Adolescence and Transition

Puberty and adolescence are defined by growth and change—physically, physiologically, and psychologically. The onset of puberty signifies the beginning of adolescence and initiates the musculoskeletal development that is familiar to all. This is anticipated around the age of 11 years in girls and about 1 year later in boys. Genital development is most commonly measured using the sexual maturity rating (Tanner stages)—tracking development from pre-pubertal (stage 0) through to full development (stage 5).¹

Urogenital conditions encountered include new diagnoses such as previously untreated hypospadias or undiagnosed disorders of sex development and the long-term management of any of the conditions described in this book.

The measurable physical changes are accompanied by major psychological and psychosocial development. The increased self-awareness and desire for independence creates important questions that a urologist must develop the skills to answer. These will relate to a patient's condition, treatment, and relationship to normality.^{2,3} The increased understanding and participation in the individual's own health care represents an important part of transition. This is the set of principles that governs the move from care in a pediatric setting to adolescent and adult health care.

Transition is a multi-faceted process designed to encourage a patient who is able to accept full responsibility for medical decision making and care with an adult urological care team. Many recommend beginning the process of transition at around the age of 12 years (or earlier) to provide ample time for all parties involved to develop the skills and understanding required by age 18 years. Many tools for the transition and additional information can be obtained online (gottransition.org).

While the basis of this chapter is to discuss genital anomalies in adolescence, our analysis and recommendations necessarily extend into adult life. The general philosophy is to avoid elective genital operations with risks to future sexual function or fertility until a time at which the patient is able to give his or her own informed consent.

9.2 Hypospadias

9.2.1 Introduction and background

Studies conducted in the mid-to-late 20th century investigated the impact hypospadias plays on the development of adolescence. Data suggested that genital appearance (pubic hair development and penile length), testicular size, and age at ejacularche were normal for hypospadiac patients with normal karyotypes (Level of Evidence [LOE] 4).^{4,5}

9.2.2 Functional outcomes in adulthood

Data concerning functional outcomes are limited (LOE 4). There remains substantial variation in initial assessment and technique, as well as cultural differences as they relate to penile length and circumcision status.

9.2.2.1 **Cosmesis**

Surgeon and parent assessment of cosmetic outcome markedly differs from patient assessment. Dissatisfaction with phallic appearance is reported 20–30% of the time.⁶⁻¹⁰ This rate increases to 75% in some cultures, most commonly related to penile size and residual chordee.^{11,12} Approximately one-third of young hypospadiac men report a desire for improved cosmesis: the underlying problem is a perceived lack of penile length, which is not surgically treatable unless associated with chordee or scarring. A standardized assessment of cosmesis hypospadias objective penile evaluation for patients with hypospadias now exists as an adjunct to the validated self-appraisal instruments hypospadias objective scoring evaluation and pediatric penile perception score.^{13–15}

9.2.2.2 Urinary symptoms

Spraying, post-void dribbling, and downward deflection of urinary stream seem to be more prevalent among repaired hypospadiacs in adolescence or early adulthood (LOE 4).¹⁶

Spraying is the most commonly reported complaint $10-63\%^{6,17}$; the majority report an incidence of $40-50\%^{.79,18-20}$ In men who had undergone a modified Bretteville repair, improvements including decreased spraying, increased HOSE score, and flow rate were noted over a 5-year study period; the reason for these improvements remains unclear, but may relate to penile growth in adolescence (LOE 3).²¹

Post-void dribbling is reported by 20–40% of adolescent and adult hypospadiacs.^{6,12,17,18,20,22} Combined lower urinary tract symptoms among those repaired in childhood is shown in **Table 9-1**.²³ In this analysis, self-reported post-void dribbling did not differ from controls.
Fewer studies present quantitative data using uroflowmetry, and most of these have been conducted in pre-pubertal children.^{24,25} Only one small long-term study suggested a substantial effect on uroflow.²⁶ Hypospadiac men have a lower Qmax at all bladder volumes, regardless of repair, meatal location, or age at surgery.²⁷

	LUTS n/N, (%)	Dissatisfied with urinary function n/N, (%)	Spraying n/N, (%)	Deviation of urinary stream n/N, (%)	Post-void dribbling n/N, (%)	Weaker urinary stream n/N, (%)	Straining n/N, (%)	Sitting during voiding n/N, (%)	Qmax%	Qmax <95% percentile n/N, (%)
Total hypospadias	77/21 7 (35.5)	56/150 (37.3)	245/818 (30)	69/267 (25.8)	104/351 (29.6)	36/239 (15.1)	15/210 (7.1)	15/174 (8.6)	24.4	36/265 (13.5)
Severe hypospadias	24/62 (38.7)		46/106 (43.4)		20/52 (38.5)	7/87 (8.0)	12/52 (23.1)	5/71 (7.0)	21.1	5/36 (13.9)
Controls	30/19 6 (15.3)	13/189 (6.8)	17/231 (7.4)	9/81 (11.1)	16/81 (19.8)	34/151 (22.5)		6/38 (15.8)	30.3	4/138 (2.9)
p (total hypospadias vs. controls)	<0.01	<0.01	<0.01	<0.01	NS	NS	N/A	NS	<0.01	<0.01

TABLE 9-1Lower urinary tract complaints and data among patients with hypospadias in
adolescence and adulthood as reported by Rynja *et al.*23

NS, not significant.

9.2.2.3 Erection/ejaculation

There are very limited data evaluating erectile function in patients with hypospadias. Existing reports are limited by small numbers of patients (particularly with proximal hypospadias) where chordee is noted as an impediment.^{6,10,28} Even when artificial erection is used during initial hypospadias repair, recurrent chordee impairing sexual life after puberty is well described.^{29,30} This complaint is most commonly reported during puberty, when penile length increases (LOE 3).³¹

Ejaculatory problems were also more prevalent than in controls (up to 37%).^{6,7,16,32} These problems are typically reduced propulsion, spraying and (less commonly) anejaculation. The etiology of a weak ejaculate may be lack of normal corpus spongiosum, with loss of elasticity in a reconstructed urethra or a urethral stricture. In reconstructions with hair bearing skin, ejaculatory problems are also common. Urethral diverticula or sacculation and less commonly pooling in a persistent urogenital sinus, as well as retrograde ejaculation or scarred ejaculatory ducts should also be considered.

One study reported erectile problems in 24% of patients.³³ Problems with erectile quality or sustainability have not been reported in hypospadiac adolescents and young adults—data are limited—and validated questionnaires have not been used.^{6,10,32}

9.2.2.4 Endocrine function

Testicular volume, follicle-stimulating hormone (FSH), and serum testosterone are related to severity of hypospadias and prior bilateral undescended testes (UDT).³⁴ Even among men with mild hypospadias and no prior UDT, data suggest a risk of hypogonadism for men with hypospadias (LOE 2–3),^{35,36} suggesting an awareness for the need for endocrine and testicular assessment (LOE 3).

9.2.3 **Primary repair in adolescence and young adulthood**

While correction of distal hypospadias had previously been considered mostly a cosmetic procedure, uncorrected hypospadiacs appear to be at risk for urethral problems in adolescent and adult life (LOE 3).^{37,38} These include chordee and urethral stricture, often related to lichen sclerosus.³⁸ Primary repairs in adulthood show a higher incidence for urethral complications (10%–50%) when compared with those in infancy where standard techniques are used.^{39–43} This rate far exceeds early complication rates when similar repairs are used in infancy—a reporting bias may explain this. In particular, tube grafts demonstrate very poor outcomes after puberty,^{37,44} thus staged reconstruction is more often used by adult urethral surgeons.⁴⁵ The tubularized incised urethral plate repair has been reported with good success among primary repairs in a post-pubertal population,⁴⁶ but demonstrates poor outcomes in secondary repairs in similar age groups.^{26,47}

Re-operation rates are poorly recorded in hypospadias series. Recent data suggest that for those repaired in infancy the rate is up to 24.1%, with less than 50% occurring within the first year—reinforcing the need for long-term follow-up.⁴⁸

9.2.4 Surgery for late complications

Patients with hypospadias—both previously repaired and unoperated, frequently present with late urinary complications.^{37,38} The "hypospadias cripple" presents the greatest surgical challenge—these patients are subject to the highest complication rates.⁴⁹ Some report up to 50% of patients experiencing complications, many occurring after puberty.⁵⁰ Reported complications include cosmetic issues, chordee, fistulae/diverticula, foreign material in the urethra (typically hair/stone), and recurrent stricture—surgical therapy must be tailored to the complication.

Treatment options for recurrent stricture should be based on the location and length of the stricture as well as the time from repair to presentation. Early strictures tend to be anastomotic and demonstrate better likelihood for patency after endoscopic management.⁵¹

The popularization of oral mucosa-free grafts (OMG) in repair of hypospadias cripples has revolutionized their treatment.⁵² Oral mucosa-free grafts have the following advantages:

- ease of harvest,
- quality of substrate for urethral substitution,
- low late complication rate, and
 - low long-term donor site morbidity.^{53,54}

One-stage onlay or two-stage repairs are preferable to one-stage tubed repairs, resulting in fewer complications with durable results in all patients.^{39,45,55–60} A two-stage approach for peri- and post-pubertal hypospadias cripples offers better outcomes.^{61,62} Even after successful repair, cosmesis remains a challenge, with one-third of patients undergoing OMG reconstruction stating that they are very or somewhat dissatisfied with the outcome.⁶³ Erectile function has been characterized using the International Index of Erectile Function 15-item questionnaire (IIEF-15), demonstrating excellent results. However, ejaculatory complaints remain prevalent.⁶⁴

9.2.5 **Psychosexual development in adolescence and adulthood**

Psychological studies examining the development of young men with hypospadias (both corrected and uncorrected) have typically used interview-based data collection (LOE 3–4). Among young men with hypospadias repaired in childhood, some authors report greater shyness, enuresis, neurotic symptoms (depression, anxiety) and delayed sexual debut.^{5,65–67} Others, however, reported no differences between repaired hypospadiacs and controls with respect to psychosocial adjustment,^{68,69} although these men were more likely to negatively appraise their genitalia and express a desire for cosmetic improvements than controls—this is independent of circumcision status or cultural background (LOE 3).^{6,70}

Neither self-, parent, nor surgeon appraisal of genital cosmesis correlates with later sexual function.^{28,66,67} However the appraisal by an adolescent is substantially lower than by a surgeon, suggesting the importance of long-term patient-reported quality of life and functional outcomes.^{10,71,72} Parent appraisal of cosmesis and of overall patient psychosocial well-being is substantially lower than patient self-appraisal (LOE 3).⁷³

Given the prevalence of genital dissatisfaction in this group and the reluctance of young men to seek medical care to address these issues,^{10,70,74} screening at the time of adolescence is warranted.

9.2.6 **Fertility**

In a Danish registry study of young male conscriptees, semen parameters did not differ between men with isolated hypospadias and controls; however, those with hypospadias and additional genital abnormalities had smaller testes and significantly poorer semen parameters (LOE 2). Surprisingly, lower paternity rates and increased rates of seeking treatment for infertility were noted among men with isolated hypospadias, raising the possibility of problems related to semen delivery or factors not accounted for by semen quality alone.⁷⁵

9.2.7 **Recommendations**

- Patients with hypospadias should undergo both subjective and objective assessment at completion of puberty using standardized methods to document cosmesis; recording meatal position, chordee, scarring, hair distribution, scrotal morphology, and genital satisfaction (Grade of Recommendation [GOR] B/C).
- Standardized urinary symptom measurement tools should be employed after puberty in patients with hypospadias (GOR B).
- All adult patients with hypospadias undergoing further urethral surgery should be warned about the need to assess and correct chordee. This should be assessed peri-operatively (e.g., artificial erection) (GOR D).

- Hypospadiac men should undergo testicular exam and screening for hypogonadism in adolescence and adult life—endocrine advice should be sought as appropriate (GOR B).
- Ejaculatory problems should be assessed after the patient has become sexually active (GOR B). Semen analysis and urethrography should be employed for men complaining of weak ejaculate to assess for urethral sacculation/diverticulum. For men with anejaculation, post-coital semen analysis and/or transrectal ultrasonography should be offered to assess etiology and treatment possibilities (GOR D). Standard guidelines regarding assessment and treatment of infertility should be followed.
- "Hypospadias cripples" as defined, should be referred to a centre of excellence for management.

9.3 Exstrophy and Epispadias

9.3.1 Introduction

Cloacal exstrophy (CE), classical exstrophy, and epispadias are conditions on a spectrum of abnormalities of the bladder, genitalia, pelvis, and, in the case of cloacal exstrophy, several other organs. The very rare condition of cloacal exstrophy is beyond the scope of this chapter. The genital anomalies in exstrophy and epispadias are the same, but may be less severe in the latter. Indeed, in babies born with very minor epispadias, there may be almost no genital anomaly at all. This chapter describes the typical exstrophy anomalies.

9.3.2 Males born with exstrophy

9.3.2.1 **Genital anatomy**

The detailed anatomy of the exstrophy pelvis and penis have been investigated clinically, by cavernosography, computerised tomography (CT), magnetic resonance imaging (MRI), by experimental models, and by dissection.⁷⁶

The pendulous part of the penis is short, as the corpora cavernosa are shorter than normal (**Figure 9-1**). Magnetic resonance imaging investigation of the normal and the exstrophy penis has established that the total corporeal length is 60% greater in normal men (16.1 cm vs. 10.1 cm in exstrophy). Most

of this deficiency is in the pendulous part of the penis (12.3 cm normals vs. 6.9 cm exstrophy). The crura are similar in length for both (3.9 cm vs. 3.2 cm). The mean corporeal diameter is 1.0 cm in normal men and 1.4 cm in exstrophy men. The abnormalities may be exaggerated by recession of the suprapubic area (**Figure 9-2**), absence of the mons pubis, and normal scrotal size.

The pubic bone diastasis is important; penile length is greater if this is ≤ 3 cm and shorter if it is ≥ 4 cm. Pelvic closure performed in infancy may be effective in producing a normal penis, at least in childhood. Currently published data suggest that the Kelly operation, which may give an excellent result for bladder function, results in suboptimal cosmesis of the penis and abdominal wall compared with other techniques.⁷⁷

FIGURE 9-1 Clinical photograph of the adult flaccid exstrophy penis





Clinical photograph of an exstrophy penis illustrating the recession in the mons area (arrowed)



The prostate is present. In adult men, the prostate is of normal weight for age but lies completely behind the urethra. The verumontanum, which is normally positioned, is a useful landmark for surgery in later life.

The shape of the erect penis depends on the initial reconstruction. In the natural state, the erect epispadiac penis has a tight dorsal chordee of varying severity (**Figure 9-3**). Cavernosography in these cases shows the site of the maximal curvature at the point where the corpora emerge from the pubic rami.⁷⁸

Penetrative intercourse may be possible, depending on the severity—couples may need advice on ideal positions.

FIGURE 9-3 Clinical photograph to show dorsal chordee in exstrophy



The corpora are of equal size at birth but may be damaged during either primary or revision reconstructive surgery. Twenty-eight cases of complete or partial penile loss have been reported, 24 after exstrophy closure and four after radical penile reconstruction.⁷⁹

Awareness of the erectile problems and appropriate reconstruction in infancy may improve function in adults. The techniques for children reviewed by Snyder⁸⁰ do produce a short but normal penis with a normal angle of erection. Perovic *et al.* reported that the penis in infants is similar in length to that of normal boys although slightly different in appearance.⁸¹ Even in adolescents and adults, correction of chordee may offer a slight increase in length.

In adult exstrophy patients, at present, the pubic area is nearly always recessed from the uncorrected pubic diastasis. The pubic hair lies on either side of the midline. Many exstrophy patients find the appearance distressing and try to hide it from their partner. It is important, either in infancy or adolescence, to rotate hair bearing flaps of skin and fat to cover the midline defect.

9.3.2.2 Sexual function

There is no reason why in exstrophy patients tumescence should not be normal. In a comparison with normal men, 11 of 19 (58%) exstrophy patients had erectile dysfunction on the IIEF-15, while the incidence in controls was 23%. Interestingly, virtually all patients had normal frequency and rigidity of erections. The dysfunction was mainly related to inability to maintain an erection and to penetrate.⁸²

Exstrophy patients presenting with erectile dysfunction should be investigated following existing guidelines for unaffected men. The only difference is that there is no cross-circulation between the corpora. Therefore, if intra-corporeal prostaglandin is to be used, each corpus must be injected individually. Occasional boys appear to have suffered damage to the erectile nerves during pelvic dissection, and report lifelong inadequate or absent erections. In patients with erectile dysfunction, a trial of standard medication such as sildenafil would be reasonable.

Masturbation is virtually universal in all reported series. In a review of the literature from 1974 to 1997 including 134 men from eight series, 101 (75%) were able to ejaculate, occasionally producing as much as 5 mL of ejaculate. Some patients describe a more or less continuous urethral discharge of semen-like fluid.⁸³⁻⁸⁵

Fear of rejection by a partner because of visible penile anomalies remains the most common problem among men with exstrophy. There is no easy solution, and much may depend on the environment in which the man lives—e.g., this may be exacerbated in cultures where sexual activity outside of an established relationship is more prevalent.

In a series from Switzerland, follow-up was available on 21 male patients born between 1937 and 1968, with a mean age of 50 years at follow-up. Nineteen of 21 patients were or had been sexually active and 16 had been married. Only 56% described their intercourse as satisfactory. The main cause of dissatisfaction was the dorsal chordee. Adolescent sexual activity was similar to that of a survey of Swiss men from a later generation published in 2002.⁸⁶ This is probably the longest available follow-up, but other groups give very similar figures with about 75% of men co-habiting.⁸⁷

Some exstrophy patients fear discovery of their abnormality and complain that they are excluded from socializing with their peers as a result. In a case-control study of adolescents with bladder exstrophy (BE) and kidney stones, exstrophy patients demonstrated more avoidance behaviours (avoiding undressing in front of or discussing their condition with peers), and reported greater concerns regarding their genital condition or possibility of "normality" or fertility in later adult life.⁸⁸ Inhibition from engaging in sexual activities outside of a well-established, trusting relationship may be a cause of distress to some adolescents and young adults with exstrophy, although patients reported by Ben-Chaim *et al.* were said to have random and short-term relationships.⁸⁹

Pressure may be put on surgeons to make the penis bigger—but it is vital not to raise false hope. Chordee and other erectile deformities can be corrected, but there is no surgical means of producing the long, normal penis for which these patients hope. Management needs to be informative and supportive, with surgery reserved for those with specific functional problems.

There have been several reports of the use of phalloplasty in men who consider their penis to be inadequate. In 2001, de Fontaine and colleagues reported the first case of radial artery free flap phalloplasty for a man with exstrophy. The natural penis was incorporated within the new phallus, with the glans and urethra emerging close to the base on the dorsum. A single inflatable prosthesis was inserted at a second operation.⁹⁰ A recent series of 10 patients (8 BE, 2 CE) undergoing radial forearm free flap phalloplasty for inadequate penile length reported all patients with gross and erogenous sensation and ability to achieve orgasm, but high complication rates with prosthesis implantation—2 of 5 devices were ultimately removed because of erosion.⁹¹

Six patients have been reported from France, with a mean follow-up of nearly 10 years. Five were said to be fully satisfied with the size and appearance of the phalloplasty and reported cutaneous sensation. Only three had regular sexual intercourse.⁹² The surgical complication may be nearly 50%. It takes a year or more for even cutaneous sensation to return to the neophallus and only then can a penile prosthesis be inserted, of which up to half have to be subsequently removed for erosion or infection⁹³ True sensation, phallic function, and sexual satisfaction are difficult to evaluate, and remain to be elucidated in future studies.

A multidisciplinary team is important for establishing that there is a genuine functional problem, rather than relationship or psychological issues requiring a different approach.

9.3.2.3 Fertility

The testes are presumed to be normal at birth in exstrophy—data to support this are lacking. There may be an increased incidence of undescended testes, being reported in six of 26 neonates (23%). However, the structural integrity of the testes and epididymides suggests an anatomical rather than endocrine association.⁹⁴

Little is known about semen quality, except in those presenting with infertility. A literature review in 1998 included 66 adults who had had semen analyses for a variety of reasons (**Table 2**). Historically, between a third and a half of men who were trying to father a child were successful.

Semen Analysis	n *
Azoospermia	32
Poor	1
Good	14
Paternity	19
Total Number	66

TABLE 9-2 Literature search results for semen analysis in adults born with exstrophy (87).

Assuming normal testes at birth, infertility may be caused by secondary leukospermia causing poor semen quality, scarring of the seminiferous tubules from chronic inflammation, or by failure to deliver sperm to the partner's cervix.

Urine infections and epididymitis are common in men with bladder exstrophy. In a recent series, six of 17 patients were reported to have epididymitis. Seven of the 17 had azoospermia, but this finding was not correlated with the epididymal findings.⁹⁵

9.3.2.4 **Ejaculatory function**

The necessary reconstruction of the urethra and absence of normal bulbospongiosus and encircling musculature mean that the normal propulsive component to ejaculation is impaired. Reconstruction of the bladder neck may result in obstruction of the ejaculatory ducts. The reported incidence of normal ejaculation varies, but for the reasons described it is at risk.⁹⁶

If there is an ejaculate containing reasonable numbers of sperm, natural insemination may be possible. Alternatively, couples can be taught a simple form of artificial insemination—the man collects his ejaculated semen in a 10-mL syringe and deposits it in the vaginal vault during days 12–16 of the female partner's menstrual cycle.

The management of male factor infertility has been radically changed by assisted fertility techniques—these apply equally to men with bladder exstrophy.⁹⁷

9.3.3 Females born with exstrophy

9.3.3.1 Genital anatomy

The pelvis has the same orientation as in men. The ovaries and uterus are normal. However, uterine supports are deficient, such that even in the nulliparous woman, the cervix is low and close to the introitus. The MRI appearances of the pelvis in women are similar to those in men. Comparing the MRI in adult female patients with exstrophy to age-matched normals, several differences are found. The most important functional difference is the deficient pelvic floor, with lateral deviation of the levator ani muscle. In exstrophy, most of this muscle is in the posterior perineum. The levator hiatus is twice as wide as in normal women.^{98,99} The two sides are more divergent and flatter, giving less support to the vagina and bladder—this gap appears to widen with maturity.¹⁰⁰ These abnormalities probably contribute to the high incidence for pelvic organ prolapse in exstrophy. Unfortunately, osteotomy does not reduce the risk for prolapse, which is primarily related to the extent of the original diastasis.¹⁰¹

In the perineum, each orifice is displaced anteriorly. If there is a urethra, it is seen on the lower anterior abdominal wall. The anus is in the position of the normal vaginal introitus. The vagina lies almost horizontally, parallel to the floor when standing. It is shorter than normal, being seldom more than 5 or 6 cm in length but of normal calibre. The introitus is narrow, not because of a hymen but from a substantial bulk of tissue—probably a continuation of the posterior vaginal wall (**Figure 9-4**). For most girls, this tissue will need incision, gradual dilatation, or reconstruction before intercourse is possible. The labia are poorly formed and do not fuse anteriorly to form a fourchette. The clitoris is usually bifid, despite earlier reconstruction. The distribution of pubic hair is the same as that seen in men.

FIGURE 9-4

Clinical photograph of the perineum of a woman born with exstrophy. There is a foley catheter in the urethra and a probe in the introitus. Note the rudimentary labia and the long distance between the introitus and the anus.



9.3.3.2 **Reconstruction of the genitalia**

At least 80% of women require genital reconstruction in puberty or early adult life.¹⁰² The objectives are to open the introitus, to unite the two halves of the clitoris, and to fuse the anterior ends of the labia to create a fourchette. It is not easy to move the vagina posteriorly to its usual anatomical position, but labial and pubic reconstruction disguises the abnormality very well. With complete soft tissue mobilization of the urogenital complex, especially if done in early childhood, it is possible to achieve a more anatomically correct outcome.¹⁰³

The introitus is characteristically narrow and can be very hard to identify, even in adults, and may be mistaken for a urethra. The vagina above the introitus is of normal calibre. To open it, an episiotomy incision or a Y-V advancement flap posteriorly from the introitus will create a wider opening—allowing penetration. It is usually possible to close the vaginal mucosa to the perineal skin directly (**Figure 9-5**).

FIGURE 9-5

Clinical photograph of the same patient as in Figure 9-4. The introitus has been opened, and a speculum demonstrates the normal vagina above.



Cervellione and colleagues describe a longitudinal incision of the vagina alone and laying in of a perineal flap. This is their operation of choice, but the rationale is not clear. The results in all but one of their 29 cases were good, regardless of the technique used; there were no data about sexual function.¹⁰⁴

The two halves of the clitoris (assuming that they can be identified) and the anterior ends of the labia are united to make a fourchette. The labia are short in anterior/posterior aspect and usually need re-alignment alongside the introitus.¹⁰⁴

The greatest difficulty is with the clitoris. It is bifid at birth. It is possible to unite the two halves in infancy. A good cosmetic result has been reported in all of 9 children in one series, but the longest follow-up was a year. No functional outcome data are available.¹⁰⁵

Discussion about surgery in childhood continues. Parents may be satisfied with a better appearance and there may be improved self-esteem, but cosmetic surgery is not essential at that time. Adults with congenital adrenal hyperplasia who had clitoral surgery in childhood have shown considerable reduction in erogenous sensation and loss of orgasmic ability.¹⁰⁶ In a very small study, one of eight adult women with exstrophy undergoing clitoroplasty had the same result.¹⁰⁷ In a series of 26 children with exstrophy who underwent clitoral reconstruction, three suffered partial clitoral atrophy.¹⁰⁸

9.3.3.3 **Procidentia repair**

The defective pelvic floor, open pelvic ring, and poor uterine supports predispose women to prolapse. In some cases, total procidentia is seen—even in nulliparous women.¹⁰⁹ The risk for prolapse is around 52%, with 85% opting for surgical treatment.¹¹⁰

Reconstructions that create near-normal anatomy may reduce the incidence for this complication. None of nine patients who had had the Kelly operation had prolapsed (compared with two of three in the same series who had had a different reconstruction), though some of the patients were barely into puberty.⁷⁷

Several techniques have been reported for the repair of this difficult condition. Hohenfellner advocates fixation of the uterus to the anterior abdominal wall in childhood. This is said to prevent prolapse but still allow normal pregnancy.¹¹¹ Two women were able to have normal pregnancies without prolapse, while one of two women who did not have a fixation had 'slight prolapse' after delivery. All deliveries were by Caesarean section. This 'prophylactic surgery' may well be helpful. However, once prolapse has occurred, there is no evidence to support the effectiveness of anterior fixation.

Although hysterectomy or partial hysterectomy has been advocated in occasional patients in the past,¹⁰² logically the uterus is the only solid organ in the pelvis that has any hope of filling the large defect in the pelvic floor.

The most successful procedure is the Gore-Tex wrap. The sacral promontory is exposed. A strip of Gore-Tex is sutured or screwed to the periosteum. The end is passed around the cervix through the base of the broad ligament and brought back to the sacrum. This procedure has been successful in up to 75% of patients, with a mean follow-up of 8 years—risks of infection and erosion are reported. Other techniques including colposuspension and hysterosacrocolpexy have been reported, but outcomes are less clear.¹¹⁰

9.3.3.4 **Female sexual function**

Even in normal women, there is very limited literature on sexual function—definitions have been poorly defined. Most series are confined to expressions of global satisfaction—although validated scores now exist, they have not been widely employed in patient groups with congenital anomalies. The results of vaginal reconstruction in exstrophy appear to be satisfactory.

There is no large or scientific survey of sexual function. Three series with reasonable numbers cover 43 patients, but they represent only about 20% of the women recorded in the relevant institutional databases.^{102,112,113} Thirty-four (79%) had regular intercourse and 10 of them had dyspareunia (29% of those having regular intercourse). Later series suggest this rate may be higher, suggesting a rate of 40–65%.¹⁰⁷ Individually, it would appear that libido is normal; the age of sexual debut is 19.9 years; and 13 of 22 (59%) who were specifically asked had regular orgasms.

9.3.3.5 Fertility

Deans *et al.* reported 4 of 19 patients achieving fertility naturally within 1 year. The remainder were delayed or required fertility treatment. This suggests that women with bladder exstrophy may suffer difficulty with fertility; this seems most likely to result from tubal obstruction or some other genital complication following surgical reconstruction.¹¹⁴

9.3.3.6 **Pregnancy and delivery**

On review of 57 pregnancies in 19 women, 21 miscarriages were reported—the authors acknowledge that this may be an overestimate as a result of false positive pregnancy tests (associated with enterocystoplasty), but it is greater than that expected in the unaffected population.¹¹⁴

With modern obstetric care, pregnancy and delivery should be uncomplicated, except for the risk for prolapse, at least as far as the exstrophy is concerned. In a combined series of patients, 43 pregnancies in 28 women were identified. Four ended in spontaneous and four in therapeutic abortion. There were 34 live births and one intrauterine death of twins.^{102,115,116} There is a high incidence for breech presentation at 57% compared with 4% in normal women.¹¹⁵

Pregnant women born with exstrophy should be under the joint care of a urologist and an obstetrician. In patients delivered in centres where appropriate support was delayed, the risk for still birth or infant mortality was increased. A decision about the mode of delivery depends on bladder drainage and continence mechanism, the nature of the reservoir, and, with an intestinal reservoir, the anatomy of its blood supply. The worst outcome is with an emergency cesarean. Most centres recommend an elective cesarean.^{114,117} See **Table 3**.

	Singleton Pregnancies N=54	Twin Pregnancies N=3
Live Birth	31	3
Miscarriage	21	
Termination	1	
Still Birth	1	3

TABLE 9-3 Outcome of 57 pregnancies in 19 women with bladder exstrophy (114).

9.3.3.7 Recommendations

Non-essential genital surgery, in both sexes, should be deferred until the patient is at least experienced enough to understand the implications and potential complications of surgery and ideally be able to articulate his or her own problem with sexual function (GOR D).

Male erections should be assessed on the basis of ability to have penetrative intercourse, or, if not commenced, consider artificial erection under anesthesia or MRI. Correction of dorsal chordee may be necessary. Erectile dysfunction should be assessed and treated within standard guidelines.

Penile length is predictably reduced with wider girth. There are no recognized lengthening procedures. Phalloplasty may be appropriate for a few severely affected patients (GOR D).

Fertility may be reduced due to poor semen delivery, hypospermia (particularly when concurrent UDTs are involved), and leukospermia. Patients should be offered semen analysis upon sexual debut and advised to use latex-free barrier contraception.

Female patients with prolapse should be managed conservatively until childbearing is completed; hysterectomy should be avoided without specific (medical or oncological) reasons, while sacrocolpopexy appears to be effective. Current, limited experience favours Gore-Tex wrap techniques (GOR D).

Dyspareunia may be helped by introitoplasty—but should otherwise be managed conservatively.

Pregnancy should be managed under the shared care of a urologist and a high-risk obstetrician—with elective cesarean section as the likely mode of delivery (GOR D).

9.4 Adolescent and Adult Care for Women with Cloacal Malformations

9.4.1 Introduction

Persistent cloaca is a congenital malformation defined by a common channel connecting the urethra, vagina, and intestinal tract to a single perineal orifice. It affects only girls and represents approximately 10% of all anorectal malformations in female patients.¹¹⁸ The incidence is reported at 1 in 50,000.^{119,120} Mortality rates are highly dependent on the variation of the cloaca and associated malformations.^{119,121} The condition's rarity and heterogeneity in presentation has created a majority of published literature that are descriptive or retrospective studies,^{119,122,123} with the largest study including 490 patients coming from the updated Peña series. To date, there is only one published prospective study with 10 patients.¹²⁴

9.4.2 Spectrum of disorders

Clinically, these patients are divided into two main groups depending on the length of the common channel (1–10 cm).¹²⁶ More than half of the patients have a channel less than 3 cm in length; this is easier to reconstruct, with a lower incidence for associated malformations. Patients with a common channel \geq 3 cm have a more complex anatomy requiring increasingly complicated reconstructive surgery with worse functional outcomes. The sinus most commonly opens near the clitoris. A posterior cloaca with an opening at the anal position is less common.¹²⁷

The most common associated malformations with persistent cloaca are the urinary tract, genitalia, spine, heart, vascular system, and gastrointestinal tract. These need to be considered when assessing a patient for further reconstruction. Anomalies in the kidneys occur in more than 60% of patients with renal agenesis, renal dysplasia, pelvo-ureteric junction obstruction, and duplex systems most frequently reported.^{121–123,128} Bladder and renal function can be affected early due to structural abnormalities in the bladder/bladder neck and/or sacral dysplasia.^{121–123,128}

Anomalies of the clitoris, vagina, and uterus can be present^{129,130}; their incidence increases in patients with a long channel or posterior cloaca. Absent labia minora and clitoral hypertrophy have been reported. Hydrocolpos, from retrograde urine drainage into the vagina, is seen in 30% of cases.¹³¹ Sixty percent have some degree of septation of the uterus and vagina,^{130,132} and 40% have double Müllerian systems with two hemiuteri and two hemivaginas, which can be asymmetric. At puberty, this defect may give rise to hematocolpos or retrograde menstruation.¹²²

In infancy, the most severe cases require an abdominal and perineal or posterior sagittal approach.^{118,119,133} In the posterior sagittal anorecto-vaginourethroplasty (PSARVUP) described by Peña,¹³⁴ the rectum is mobilized from a posterior perineal approach and the vagina is dissected and mobilized from the urinary tract. All three components are separated and placed in their normal

positions, where the common channel will form the urethra. The complicated part of the repair is to separate the anterior vaginal wall from the urethra, and in 1997 Peña presented the total urogenital mobilization.¹³⁵ Here, the rectum is mobilized as in PSARVUP, but the entire urogenital sinus is mobilized down to perineum en bloc. The technique can be used for channel length of up to 5 cm and is less time-consuming, reduces the risk for vaginal and urethral stenosis, and gives a better cosmetic result.^{122,126,136,137} A cloaca with a short channel of ≤ 3 cm can be repaired using posterior sagittal approach with a relatively short, reproducible operation. Patients with a longer channel of >3 cm will usually require a laparotomy, have a higher incidence for urological problems to be addressed, and often require special manoeuvres for vaginal reconstruction.¹²⁶ To avoid laparotomy, laparoscopic-assisted techniques have been described.¹³⁸ In cloacal repair, it may be useful to visualize the internal gynecological anatomy for diagnostic purposes and to mobilize the rectum in cases of high implantation of the rectum in the vagina.¹³⁸

It has been proposed to postpone vaginoplasty until puberty.¹³⁹ The advantages of a well-motivated patient, well-estrogenized tissues following puberty, and the possibility to use more conservative methods such as self-dilatation appear to be outweighed by the need for remobilization of the rectum and the need to work through previously scarred tissues,^{129,130,132} supporting the view that all aspects of the cloaca should be addressed at the same time. In 90 cases of 490 cloacal reconstructions, the rectum, colon, or small intestine was used as vaginal replacement in a report from Levitt & Peña.¹²² A "vaginal switch" has also been described for a patient with two large hemivaginas high in the pelvis, where one hemiuterus was resected and switching of the dome of the corresponding hemivagina to the perineum, preserving native vaginal tissue.¹³¹ With vaginal substitution, high incidences for complications are reported, including bothersome mucus production, bleeding, stenosis, neovaginal prolapse, fistula formation,¹⁴⁰), and malignancy.¹⁴¹

As discussed, bowel is used for vaginal substitution in girls with cloaca. Different dilatation methods are difficult due to the malformation but may be tried in selected cases beyond puberty. Oral mucosa graft is described—though not specifically in cloacal anomalies—and may be useful, especially when correcting a stenotic, scarred introitus or performing revision surgery in the older girl, though the literature remains sparse.^{142,143}

9.4.3 Genital outcomes

Patients with cloacal malformations have a high incidence for gynecological anomalies that may not become symptomatic until menarche or later in life.^{129,130,132,144,145} Combining the three largest series on gynecologic outcomes,^{130,132,145} 76% of patients developed uterine function. Normal periods at puberty occurred in 38%, early puberty in 6%, but 56% of these patients presented with cyclical abdominal pain due to obstruction. The obstruction was at or above the cervix in 41%, stenosis of a persistent urogenital sinus orifice in 48%—10% were due to vaginal stenosis from previous reconstruction; all required surgery to relieve obstruction. The etiology of amenorrhoea in the 16 patients was vestigial or congenital absence of the uterus in 69%, atretic uterus in 19%, and 13% were being followed for possible obstruction. All studies concluded that long-term follow-up of these patients is warranted and that screening with examination under anesthesia and imaging with ultrasound or MRI may decrease the morbidity later in life. Adult gynecological follow-up in 21 patients determined that the majority (86%) reported an adequate vagina with normal menses and 67% were sexually active. Half of women required no further vaginal reconstruction, while the remaining half required revision or primary repair in adulthood; women with a long common cloacal channel appeared to be at higher risk of requiring surgical revision.¹³⁰ Similarly, Hendren¹¹⁹ reported that 71% adult patients have had coitus and six have had children—five by cesarean section and one vaginally. One recent case report described a woman who had triplets by cesarean section and good maternal and neonatal outcome.¹⁴⁶ Lastly, cancer in the neovagina has been reported.¹⁴¹ These cancers are reported to occur at a younger age, and the risks factors could be granulation tissue, inflammatory pseudopolyps, viral infection with human papillomavirus, or mechanical irritation from dilators.¹⁴¹

9.4.4 **Recommendations**

It is imperative that these patients have long-term follow-up with an experienced multidisciplinary team to address urinary continence, renal function, bowel continence, and sexual function (LOE 3).

9.4.5 **Gynecologic Follow-Up**

With the high incidence for cyclical abdominal pain due to obstruction (56%), we recommend that patients with persistent cloaca be evaluated by a urologist and/or gynecologist with experience in treating young women with cloacal anomalies early in puberty (LOE 3). This evaluation may include an examination and hysteroscopy to assess adequate vagina for menstruation and imaging (pelvic ultrasound, hysterogram, or MRI) to assess for obstructed supracervical structures. In addition, routine follow-up should also continue to screen for vaginal stenosis, dyspareunia, cancer screening, and future obstetric concerns (LOE 3).

9.5 **Disorders of Sex Development**

9.5.1 Introduction

It is now advocated that the term "disorders of sex development" (DSD) be used for congenital conditions with discordance of genotypic, gonadal, and/or phenotypic sex.¹⁴⁷

Treatment controversy has arisen around the timing and extent of genital surgery. Both reaction and debate are often based on retrospective data that do not reflect current advances in our understanding of the molecular genetics of these disorders, improved endocrine control, intensive psychosocial/ sexual counseling, and a stronger emphasis on informed consent for parents.

9.5.2 Incidence

The incidence of newly diagnosed DSD in adolescents is unknown. Two main groups exist—phenotypical female patients presenting with amenorrhea and, in both sexes, delayed (or precocious) puberty. Even within these groups, a DSD is an unusual diagnosis. Among the former group, 46,XY DSD—complete androgen insensitivity (CAIS)—is probably the most common cause, and mild cases of 46,XX DSD—congenital adrenal hyperplasia (CAH)—are occasionally found.

Hypogonadal hypogonadism and chromosomal mosaics sometimes have diagnosis delayed until puberty. Inappropriate pubertal development is seen in 5-alpha reductase type 2 (5α RD2) deficiency.

9.5.3 **Consequences of no treatment**

A decision on whether to treat an individual with DSD lies entirely with the patient once he or she is of an age to give consent. Genital surgery has an uncertain outcome, and it is important that the adolescent has adequate help to explore his or her own sexuality and genital function before making a decision. In some cases, the avoidance of surgery may be beneficial. As part of their consent, patients must be informed that much of the literature includes poorly and sporadically reported outcomes of previously abandoned techniques and may not be relevant to them beyond childhood. Hence, with the increasing availability of Internet access, education and re-education becomes mandatory.¹⁴⁸

9.5.4 **Investigation and care of the patient with DSD**

Depending on patient age and presentation, appropriate testing should be individually directed. Care based upon algorithms may be useful after initial testing and diagnosis is established. In adolescents, conversation can be provided directly to the patient regarding the prospects for sexual function, fertility, and the diagnosis of pre-malignant conditions in the gonads by biopsy. Psychological assessment and support is critical and should be carried out only by practitioners experienced in the field of DSD.

9.5.5 **Gender assignment**

Data are lacking and thus firm recommendations cannot be made.

9.5.6 Surgery for DSD—female phenotype

Historically poor cosmetic, functional, and psychological results have led some experts to suggest a moratorium on pediatric-aged "sex reassignment surgery".¹⁴⁹ However, early surgery may have the advantage of improved parent-child bonding, but the disadvantage of requiring revision in adolescence.^{139,150} Newer techniques have yet to be studied into adolescence.

Indications for surgery include:

- 1. Relief of obstructed menstruation
- 2. Creation of a vagina for penetrative intercourse

In adolescence, four types of surgery may be required:

Revision of previous surgery
 Clitoral reduction

- **3**. Vaginoplasty
- 0 1
- 4. Management of gonads

3. Improvement of genital appearance and

4. Improvement of psychological well-being

Revision surgery varies according to need, but most often an inadequate vagina will need enlargement. Some of the procedures may be complex and should only be undertaken in specialist units.¹⁵¹ It now has been accepted that vaginal dilation should not be introduced until after puberty.¹⁴⁷ There remains a lack of standardization.

The more that is learned about clitoral innervation, the less attractive surgery becomes. Clitoridectomy must never be done, and clitoroplasty should only be offered for more severe variants, such those with Prader >III classification. The emphasis must be primarily on function, with cosmesis an important, but secondary parameter. Anatomically driven surgery is based on the elegant work of Baskin *et al.*, who have studied the neurovascular supply of both the penis and clitoris.¹⁵² This along with thoughtful reviews, such as those by O'Connell *et al.*, have increased understanding of the clitoris and how to minimize sensory damage, thus maximizing the potential for adequate quality of sexual life/function (LOE 4).¹⁵³ It is most important to preserve the dorsal and lateral skin on and around the clitoris, which has been shown to be the most sexually sensitive.¹⁵⁴ Patients must still be made aware that surgery may still damage sexual sensation (LOE 4).¹⁵⁵

In those who have an absent or inadequate vagina, it has been advocated that vaginoplasty be deferred until the patient is older.¹⁴⁷ As highlighted in this chapter, studies in different groups show variable outcomes, though good long-term results for sexual function with bowel vaginoplasty have been reported.^{154,156}

Formal assessment of sexual function in reports of vaginoplasty has been limited. Some studies have applied standard instruments and produced valid results.¹⁵⁶ Others have relied on fairly superficial interviews. Review of the literature suggests that about 70% of women are able to have penetrative intercourse, of whom about 10% have dyspareunia.¹⁵⁷

Relatively little attention has been paid to the presence or absence of 'normal' female external genitalia and the primary influence on sensation. Where a clitoris and reasonably normal labia are present, sexual sensation is likely to be good. Where these are absent and, particularly, in 46,XY individuals raised as females, the results are more doubtful. In four recent papers, it is only possible to identify 18 such patients, of whom 6 were clearly stated to have had a good result and one had a bad result; the outcome in the other 11 patients was uncertain.^{154,156,158,159} The condition 46,XX DSD should be differentiated from other causes of vaginal hypoplasia, agenesis, or loss (e.g. Mayer-Rokitansky-Küster-Hauser syndrome), or following treatment for childhood pelvic malignancy, which is not DSD. In the patient with 46,XX DSD requiring *de novo* reconstruction, again there is little literature to support a "best" technique for a given patient. Treatment decisions will often be based on surgical experience and judgment as part of a balanced discussion in offering intervention to an individual patient.^{135,160,161} Some complex cases may benefit from considering adjunctive techniques, including the prone posterior sagittal approach (those with high vaginal take-off form common genitourinary sinus) and utilization of oral mucosa vaginoplasty (scarred revision cases in particular)143,162 A few patients with 46,XY DSD will require complete neovaginal creation similar to those with vaginal hypoplasia/agenesis. Although the pediatric urological community has favoured the use of bowel for neovaginal reconstruction, there are still no controlled data to support this over alternatives such as skin or self-dilatation.¹⁶³ Long-term evaluation of the neovagina is mandatory due to the high risk for scarring, diversion colitis, and the risk for tumour development.¹⁶⁴ Other centres have gained experience with progressive dilation methods (Vecchietti, balloon vaginoplasty) and procedures where vaginas lined with different tissues are created between the urethra/bladder and rectum (buccal, McIndoe-Reed, Davydov).^{143,165-168} Here too laparoscopy has been utilized in lieu of laparotomy in those who require a combined antegrade and retrograde approach.^{165,168}

Lower urinary tract symptoms appear more prevalent and have less chance of resolving in patients with 46,XX DSD operated on in childhood. Lower urinary tract symptoms cannot be attributed directly to either the surgery or the associated adrenal abnormality.¹⁶⁹

9.5.7 Surgery for DSD—male phenotype

The most common penile anomaly is hypospadias. It is suggested that standard hypospadias techniques be employed in any patient with DSD. $^{170}\,$

As with exstrophy, phalloplasty may be useful for some patients. Most data come from patients with gender dysphoria, whose objectives may not be same as those of a patient with DSD. In gender re-assignment patients, 91% have a successful penile construction with erections and, of those, 91% are said to have intercourse. In DSD and other patients with congenital anomalies, there are case reports of successful outcomes.^{90,171}

Tissue expanders may be useful in difficult clinical situations.¹⁷² Progress in tissue engineering is promising, but not yet a clinical reality in the field of phallic reconstruction.¹⁷³

Sexual function in a male patient with a small penis has received little study. In a series of 20 unselected patients with a variety of DSD diagnoses, all were heterosexual and 75% were having intercourse. Although other small series selected from psychology clinics have given less satisfactory outcomes, it seems likely that men with a small penis can have normal sexual function that is satisfactory, even if there are no data on the partner's view.¹⁷⁴

9.5.8 **Recommendations**

The management of the patient with DSD is lifelong. Multidisciplinary care including a gynecologist, endocrinologist, geneticist, psychologist, and other mental health workers is mandatory.

The management of the patient with DSD who reaches adolescence has not been well studied. As a result, guidelines are difficult to formulate. Transition of care to interested and qualified adult specialists must be developed and encouraged.

Dissatisfaction with gender assignment may occur at any age and change may be necessary. A small penis should not, on its own, be an indication for a female assignment.

Present evidence suggests that as much genital surgery as possible should be delayed until adolescence.

Intestinal vaginoplasty should be weighed against other surgical techniques, as none are proven above others. Long-term followup is essential.

Data on plastic reconstruction of the phallus in male patients are so limited that the technique cannot be recommended other than in very carefully selected patients treated in specialist units.

The gonads in disorders of sex development

The management of the gonads in adolescence depends on:

- 1. Their concordance with the sex of rearing
- 2. The risk for malignancy

- 4. Fertility in the sex of rearing
- 5. Patient preference
- **3**. Their ability to produce natural pubertal development

9.5.9 Sex of rearing, puberty, and fertility

By the time of adolescence, the gender of rearing already will have been established. There is known to be an increased incidence of gender dysphoria in patients born with disorders of sex development and some may wish to make a change in early adult life,²⁰⁹ but the true frequency of such an occurrence is not known.

Approximately 60% of patients with $5\alpha RD2$ who were assigned female gender in infancy and virilizing at puberty (and all those assigned male) live as males. Genetic males born with a micropenis are almost always raised as males and have normal sexual function in at least 75% of cases.¹⁷⁴

Therefore, the majority of patients have gonads concordant with their sex of rearing. Hormonal secretion will at least contribute to a natural puberty, though supplementation may be necessary. Fertility is certainly reduced in girls born with CAH, particularly salt-loosing patients, but common enough that the ovaries may be regarded as 'normal'.²¹⁰ Pregnancies in the partners of men with 5 α RD2

have been reported.^{211,212} Thus, the goals regarding the gonads are to preserve gonadal function as it pertains to sex hormone production according to sex of rearing and potential fertility, while minimizing any risks for malignancy.

In CAIS the genotype is 46,XY. However, the sex of rearing is always female, and individuals have been shown to be comfortable in adult life.²⁰⁹

Among patients with partial androgen insensitivity (PAIS), androgen biosynthetic defects, and incomplete gonadal dysgenesis, there is dissatisfaction with the sex of rearing in about 25% of individuals, whether raised male or female.²¹³

The decision on sex of rearing in ovotesticular disorder of sexual development (DSD) should consider the potential for fertility based on gonadal differentiation and genital development. In the case of mixed gonadal dysgenesis (MGD), factors to consider include prenatal androgen exposure, testicular function at and after puberty, phallic development, and gonadal location.

9.5.10 **Risks for neoplasia**

In general, an abdominal gonad harbouring a Y chromosome is at high risk for malignancy (**Table 4**) while offering poor reproductive function.²¹⁴ The testes in patients with CAIS have been carefully studied after removal at all ages. Carcinoma *in situ* has not been identified before puberty, though the earliest reported malignancy is at 14 years of age.^{215,216} Magnetic resonance imaging may represent a way of following patients who make a choice to retain their gonads.²¹⁷ Spermatogenesis has not been seen. Patients with PAIS raised female have not been studied in such detail. In both groups, the gonads usually produce enough estrogen to allow for normal pubertal development. The present recommendation is that the gonads are removed in infancy, but parents may elect to retain them until adolescence to allow for a natural puberty, deferring estrogen supplementation until adulthood.

The streak gonad in a patient with MGD raised male should be removed in early childhood.²¹⁸ Bilateral gonadectomy is performed in early childhood in females (bilateral streak gonads) with gonadal dysgenesis and Y chromosome material.

In patients with androgen biosynthetic defects raised female, gonadectomy should be performed before puberty. A scrotal testis in patients with gonadal dysgenesis is at risk for malignancy. The current recommendation is testicular biopsy at puberty seeking signs of pre-malignant lesions, such as carcinoma *in situ* or undifferentiated intratubular germ cell neoplasia. If positive, the management is sperm banking before treatment with local low-dose radiotherapy, which is curative.²¹⁹

Patients with bilateral ovotestes are potentially fertile from functional ovarian tissue.^{219,220} Separation of ovarian and testicular tissue can be technically difficult and should be undertaken, if possible, in early life.

Klinefelter's syndrome is seldom diagnosed until adolescence because the genitalia are normal. At puberty, some secondary sexual characteristics develop but the testes remain small and soft. The karyotype is 47,XXY. All are azoospermic, and testicular biopsy shows the presence of hyalinized

seminiferous tubules and Leydig cell hyperplasia. However, there is no increased risk for neoplasia, and pregnancy has been established using testicular sperm for intracytoplasmic sperm injection.²²¹ The testes undergo progressive deterioration as the young men progress through puberty, and as such some have advocated for sperm harvest and cryopreservation in early puberty to maximally preserve future fertility potential.²²² The testes should, therefore, be preserved.

The risk for malignancy is highly influential in the management of the gonads. The highest risks are in those with a Y chromosome and dysgenetic testes. The risk levels are shown in **Table 4**.

Risk Group	Disorder	Malignancy Risk (%)	Recommended Action	Numbers:		
				Patients (n)	Studies (n)	
High	GDa (+Y)b intra-abd.	15–35	Gonadectomy at diagnosis	12	>350	
	PAIS non-scrotal	50	Gonadectomy at diagnosis	2	24	
	Frasier	60	Gonadectomy at diagnosis	1	15	
	Denys-Drash (+Y)	40	Gonadectomy at diagnosis	1	5	
Intermediate	Turner (+Y)	12	Gonadectomy at diagnosis	11	43	
	17β-HSD	28	Watchful waiting	2	7	
	GD (+Y)b scrotal	Unknown	Biopsy at puberty	0	0	
	PAIS scrotal gonad	Unknown	Biopsy at puberty	0	0	
Low	CAIS	2	Removal at puberty/earlier	2	55	
	ovotesticular DSD	3	Testis tissue removal	3	426	
	Turner (—Y)	1	None	11	557	
None	5 lpha-reductase	0	Unresolved	1	3	
	Leydig cell hypoplasia	0	Unresolved	1	2	

TABLE 9-4 DSD: risk for germ cell malignancy according to diagnosis

abd.: abdominal; 17β-HSD: 17-beta-hydroxysteroid dehydrogenase; CAIS: complete androgen insensitivity; DSD: disorders of sex development; GD: gonadal dysgenesis; PAIS: partial androgen insensitivity.

aGonadal dysgenesis (including not further specified; 46,XY; 46,X/46,XY; mixed; partial; complete); bGBY region positive, including the TSPY gene (adapted from Hughes et al.²²³).

9.5.11 **Recommendations**

The prospects for fertility should be influential in advising on sex of rearing. Those with CAH have a good potential for fertility. Fertility is possible even with very inadequate gonads such as those found in Klinefelter's syndrome and 5α RD2 using assistive reproductive technology.

Gonadectomy in childhood is recommended when there is a high risk for malignancy, which includes patients with Y chromosomes and dysgenetic testes. With lower risks, gonads may be preserved until puberty is completed (see Table 7-4).

9.6 Undescended Testes

9.6.1 Incidence

Cryptorchidism, or undescended testis, is one of the most common congenital anomalies of the genitourinary system, with the incidence of 1–3% in male newborns.^{175,176} However, only about 1% of patients presents with UDT after puberty. Of the boys with cryptorchidism, 10–20% have impalpable testis which might be absent, intra-abdominal, or intra-canalicular; 40% have testes located in the inguinal canal; and 40–50% have gliding or retractile testes moving between the scrotum and inguinal canal.¹⁷⁷ The incidence of UDT in adolescence is unknown, but almost invariably represents a diagnosis missed in childhood or as so-called ascending testes.

The most common problems associated with an undescended testis in adolescents are the increased risk for infertility, germ cell neoplasia, torsion, and inguinal hernia.^{178,179}

9.6.2 **Consequences of no treatment**

Men with a unilateral UDT that is palpable in the inguinal canal probably suffer no consequences if nothing is done. Some do present complaining of crushing of the testis during intercourse.

The risk for neoplasia is higher in those with uncorrected UDT, particularly when intra-abdominal. Orchiopexy may also affect the type of germ cell tumour. If the testis is unoperated, approximately two-thirds of the neoplasms are seminomatous, whereas if the testis has been subjected to orchiopexy, nearly two-thirds are non-seminomatous.^{179,180}

Men with bilateral uncorrected UDT are very unlikely to be fertile, though advances in reproductive technology may alter this situation, and the testes often have retained endocrinologic benefit with preservation of Leydig cell function.

9.6.3 **Diagnosis of undescended testes**

No radiologic imaging is necessary to confirm palpable UDT. However, in adolescents, ultrasound or axial imaging and testis tumour markers (alpha-fetoprotein, beta human chorionic gonadotrophin, and lactate dehydrogenase) may be helpful to diagnose occult cancer in an impalpable testis. The overall accuracy of radiologic imaging including ultrasound, CT, and magnetic resonance for the impalpable testis is 44%. In boys with unilateral or bilateral undescended testes with one palpable testis, no further laboratory testing is necessary to confirm the diagnosis. In adolescents with bilateral impalpable testes, human chorionic gonadotrophin (hCG) stimulation test may be helpful to determine whether the testes are present (LOE 3).^{181,182}

Current management for adolescents with non-palpable testes is laparoscopy to confirm the presence of testes (LOE 4).¹⁸¹⁻¹⁸³

9.6.4 **Treatment options for undescended testes**

Orchiopexy is not the best treatment for post-pubertal men with unilateral cryptorchidism, as a cryptorchid testis cannot contribute to fertility in the majority, and may have a potential for testicular malignancy and torsion. Orchiectomy should be recommended for patients of adequate anesthetic risk (American Society for Anesthesiologists I-II) up to age 50 years. After age 50, risk for testicular neoplasia is less than risk for orchiectomy, and therefore observation is recommended (LOE 4).¹⁸⁴

Impalpable testes in adolescents can be managed by open or laparoscopic approaches. Abdominal testes can be managed by open trans-abdominal orchiopexy, Fowler-Stephens orchiopexy, laparoscopic or laparoscopic-assisted orchiopexy, and microvascular orchiopexy with one- or two-stage approaches.¹⁸⁵⁻¹⁸⁷ Laparoscopic orchiopexy offers less trauma of access, a rapid recovery, and minimal adhesion formation and scarring, with a 92.8% overall success rate in a multi-institutional analysis (LOE 4).¹⁸⁸

Adults with bilateral UDT present a very difficult problem. Although they are likely to have azoospermia, reproductive technology is moving forward so fast that future fertility cannot be ruled out. Every effort should be made to get one or both testes into the scrotum or into an ectopic location in the groin where the testis can be monitored by self-exam. It is in such patients that micro-vascular transfer may be indicated if all else fails.¹⁸⁹ Although some have advocated leaving the testes in the abdomen, the risk for malignancy has been estimated to be approximately 12%,¹⁹⁰ and the imaging needed over a lifetime to prove that cancer is *not* present is so complex that it makes it an unacceptable option.

9.6.5 **Undescended testes and infertility**

A testis that has not descended naturally probably produces few sperm. In two series where fertile men had a staged vasectomy, semen analysis after ligation of the normally descended side showed severely reduced parameters in 15 of 16 men (LOE 3).^{191,192}

Boys with UDT may have an increased risk for infertility, because of a decreased number and delayed maturation of germ cells, as well as progressive interstitial fibrosis.^{193,194} Nonetheless, in boys operated for unilateral UDT at any age before puberty, the incidence of infertility is not significantly different from controls.¹⁹⁵ In those operated for bilateral UDT, infertility is found in about half of men (LOE 3).¹⁹⁶

Risk factors for infertility with cryptorchidism include bilaterality, orchiopexy after puberty, and intra-abdominal location.¹⁹⁵ The combination of low Inhibin-B and elevated FSH levels with decreased sperm parameters indicates a high risk for reduced fertility.¹⁹⁵ Nearly all men with untreated bilateral UDT are infertile. However, viable sperm can be retrieved by aspiration of the testicular tubules.¹⁹⁷

In addition, two-thirds of undescended testes have an epididymal abnormality, most commonly a long looping epididymis, dysjunction of the testis and epididymis, and epididymal atresia, causing obstruction of the ducts.¹⁹⁸

A retractile testis may become an ascending or acquired undescended testis.¹⁹⁹ The effect of retractile testes on male fertility is not known. Current evidence suggests that truly retractile testes do not need either surgical or hormonal treatment.

Orchiopexy has been recommended to preserve Leydig cell function. Whether it is effective in this role is uncertain, as some men who underwent orchiopexy in later childhood have subclinically decreased Leydig cell function.^{200,201}

Impaired spermatogenesis in cryptorchidism may be partially associated with genetic abnormalities. A high prevalence of Yq micro-deletions in unilateral cryptorchid boys has been reported.²⁰² In these patients, orchidopexy probably does not improve the testicular function, whatever the age at which it is performed.

It has been suggested that a unilateral undescended testis may produce antisperm antibodies, which may cause infertility, even if the maldescent has been corrected. Current evidence is that subfertility in cryptorchidism is not due to either a trauma-induced autoimmune response or a unilateral undescended testis.²⁰²

9.6.6 **Cryptorchidism and testicular neoplasia**

The incidence of testicular cancer in men with a history of cryptorchidism ranges from 3 to 5%, a 3.7- to 7.5-fold increased risk over the normal population.²⁰³⁻²⁰⁵ The relative risk for testicular cancer in each testis in bilateral cryptorchidism is higher than in unilateral cryptorchidism. The risk of developing testicular cancer in cryptorchid men is not eliminated by orchiopexy, though it may be reduced.¹⁸⁰ The risk appears to increase with increasing age at surgical correction (a 32-fold increased risk after the age of 11 years) and reaches the highest value in men whose intra-abdominal testes have not been corrected.^{204,206} Biopsy at the time of orchiopexy also may increase the risk.^{205,207} There is a 10% incidence of testicular microlithiasis following orchiopexy, a two-fold greater incidence than in the controls (LOE 3).²⁰⁸ The relationship between the ultrasound and the microscopic findings is not known. Young men operated for UDT and found to have 'microlithiasis' on ultrasound may be at increased risk for neoplasia. There is insufficient evidence to recommend routine biopsy of such testes, but annual clinical and ultrasound examination should be performed (LOE 4).²⁰⁸ All adolescents who have had surgery for UDT should be taught how to examine their own testes and should self-examine monthly.

9.6.7 **Recommendations**

No radiologic imaging is necessary to confirm palpable UDT. Current management for adolescents with non-palpable testes is open inguinal exploration or laparoscopy to confirm the presence of testes (GOR C).

Adolescents with UDTs should undergo surgery because of the potential risks for testicular cancer and torsion. The main goals of treatment are to correct any associated inguinal hernia and to minimize the risk for torsion. The risk for neoplasia is not altered, but the scrotal position allows earlier diagnosis by self-examination (GOR B). Fertility is not altered by surgery after puberty (GOR B). Hormonal therapy is not indicated for post-pubertal cryptorchidism (GOR C).

Orchiectomy should be recommended in post-pubertal men presenting with unilateral cryptorchidism (GOR B). Orchiopexy and testicular biopsy is the treatment of choice in adolescents with bilateral undescended testes (GOR B).

9.6.8 Buried penis

Young boys who are said to have a 'buried penis' often have a normal penis beneath excessive skin, fat, and connective tissue. In younger patients, there is a suggestion that inelasticity of the dartos fascia may result in the penis being tethered and not protruding as readily as it should. There are a few who have undergone circumcision and/or progression of lichen sclerosis and the resultant scarring leads to a similar effect and penile concealment as a result—some authors have suggested that following newborn circumcision this may improve from an initially buried appearance,²²⁴ suggesting an initial conservative approach is justified.

In adolescent boys, the penis needs to be examined carefully. Gentle pressure around the penis will often push back the suprapubic tissues and reveal an underlying normal penis. This creates a dilemma for the surgeon about whether to operate and remove the suprapubic tissue. It is also possible to fix the base of the shaft to the pubic fascia and ventrally to accentuate the penoscrotal angle by fixing the subcutaneous tissue of the scrotum to the ventral surface of the penile shaft. Published series suggest that with a combination of adhesiolysis and lipectomy (suprapubic and lateral), erect length can be improved by up to 185%.²²⁵ Similar approaches in pediatric patients have highlighted the importance of avoiding circumferential incisions—suggesting the approach should be via the midline raphe to avoid subsequent penile edema.²²⁶

In assessing these patients, other diagnoses such as micropenis need to be excluded. Secondly, patients need to understand that they have a normal penis and that they will be able to have normal intercourse and fertility without surgery. Surgery should be avoided until they have completed puberty as with growth and development the suprapubic fat pad may decrease considerably. Patients should receive appropriate advice and support about diet and exercise that may help them to resolve the appearance without an operation. This does not make surgery wrong, but these steps are important to avoid operating on patients either prematurely or unnecessarily. An augmentation phalloplasty may be what is offered with a z-plasty on the lateral and penoscrotal aspects of the shaft with excision of the suprapubic fat and division of the penile suspensory ligaments. The Spyropoulos study relates to what is suggested to be micropenis but Montorsi points out in the following editorial comment that the mean stretched length was 9.12 cm, which is above that meeting the definition of a micropenis,²²⁷ therefore the argument is raised about the need for surgery at all—this is an important point and needs to be considered very carefully in these patients. In pediatric practice, preputial flaps may act as useful grafts.²²⁸ For peri- and postpubertal buried penis cases related to scarring from lichen sclerosis and/or circumcision, release of the penis with split-thickness skin graft or scrotal flap to the penile shaft with or without liposuction may be necessary.²²⁹

9.6.9 **Recommendation**

Patients should be carefully examined to establish the diagnosis. Where appropriate, dietary advice should be given to reduce surrounding tissue cover. Surgery is possible in childhood, but, if possible, deferral to postpuberty is ideal to ensure necessity.

9.7 Acquired Penile Anomalies

9.7.1 **Priapism**

Stuttering or fulminant priapism is a distressing symptom sometimes associated with sickle cell disease occurring in up to 50% of affected male patients.²³⁰ Other causes, including drug-induced (cocaine, trazodone) can be seen later in childhood and adolescents. If episodes are painful and low flow, they may result in permanent damage to erectile function. There is little evidence for a definitive treatment strategy. The principles for managing any patient sickle cell disease are important, including analgesia, oxygenation, and fluid resuscitation and should be adhered to. Early involvement of the hematology team is vital. Stilboestrol and alpha agonists have previously been tried.²³¹ Published data have suggested that finasteride may be of some benefit in reducing episodes.²³² One publication suggests that daily low-dose sildenafil may be useful in the relief of a sickle cell priapism.²³³

It is also worthy of note that in young men using cocaine, there is an increased incidence of priapism both when inhaled and applied topically to enhance sexual performance.^{234,235} There are case reports of phosphodiesterase type 5 inhibitors inducing priapism.^{236–238} These incidences appear to relate to overdosing and probably do not affect the safety of the drug. It may be that combination with some other classes of drugs enhances this small risk.²³⁹

9.7.2 **Recommendation**

Priapism in male adolescents should be assessed with a careful history of underlying systemic illness including hematological disease (sickle prep, complete blood count with differential). Recreational drug use may be causative, and a toxicity screen is recommended when the etiology is not evident by history.

9.7.3 Adolescent varicocele

9.7.3.1 **Prevalence**

Varicocele is seen in normally fertile men and in adolescents (see **Table 9-5**), but is commonly associated with subfertility in adults. By the time an adolescent has reached Tanner stage 5, there is a reported prevalence of nearly 15%—similar to that in adults but it is very rare before 10 years.²⁴⁴ Varicocele may be progressive, although evidence of cumulative damage has proved elusive (LOE 3).

TABLE 9-5 Prevalence of varicocele and associated testicular hypotrophy by age

	Prevalence of varicocele (%)	Prevalence of hypotrophic testis (%)
Under 11 years	0	0
11–14 years old	6-8	7.3
15–19 years old	11–19	9.3

9.7.3.2 Diagnosis of adolescent varicocele

Adolescent varicoceles are usually asymptomatic and recognition is often incidental. Boys should be examined in a warm room in the supine and standing positions with and without the Valsalva maneuver. Diagnostic imaging is unnecessary, except in the case of a unilateral right, non-reducing varicocele, which may represent silent retroperitoneal pathology. The classification is shown in **Table 6**.

TABLE 9-6 Classification of varicocele

Grade 1	Palpable only on Valsalva maneuver
Grade 2	Palpable without Valsalva maneuver
Grade 3	Visible without need for palpation

Measurements of testicular volume are important at both diagnosis and following treatment with either ultrasound or orchiometer.²⁴⁸⁻²⁵⁰ A discrepancy of greater than 2 mL or 20%, represents testicular hypotrophy on the affected side. Testicular consistency should also be noted during clinical examination.

Other tests such as FSH, testosterone, or gonadotropin-releasing hormone (GnRH) are of limited value, as there is considerable difficulty with relating a result to prognosis.²⁵¹ Similarly, semen analysis is only useful two or three years after puberty has begun, and there are considerable ethical difficulties in obtaining samples.²⁵² All of these tests should be reserved for boys in late adolescence who have a large varicocele and equal-sized testes (LOE 3).

9.7.3.3 **Consequences of varicocele in adolescents**

Hyperthermia, hypoxia, oxidative stress, and the retrograde passage of renal or adrenal metabolites have been the most common processes implicated in this disorder.^{253–256} These would all theoretically prove toxic to the germinal epithelium, with a negative effect on gamete production and a reduction

in testicular volume (as 90% of testicular volume is made up of seminiferous tubules and germ cells). Abnormalities of tubular histology and function are found more commonly in those with varicoceles compared with controls. And yet, the impact on male factor fertility remains controversial.

Varicocele may be associated with reduced motility and an increased number of abnormal forms (LOE 3)²⁵²; increased DNA fragmentation (which may denote poor sperm function) has also been shown.²⁵⁷ A 10% testis size difference may show an effect on sperm concentration and total sperm count. The correlation with semen parameters was most dramatic when the difference in size was 20% or greater.²⁵⁸ Ligation of varicocele may reverse abnormalities and allow catch-up growth of a hypotrophic testis.^{251,252,259} These data do not provide a direct correlation with fertility/paternity.

9.7.3.4 Indications for surgical intervention

Varicocele treatment selection remains controversial. Various thresholds have been proposed but a >20% difference in testicular size appears the most reasonable based on recent data.^{258,260}

Kolon and colleagues have shown that significant testicular catch-up growth can occur over time. The authors propose that only those male adolescents with asymptomatic varicoceles who are shown to have a significant growth discrepancy for 2 or more annual ultrasounds should be considered surgical candidates.²⁶¹ One exception to this general recommendation would be the patient with 20% difference who has already reached Tanner stage 5 development. In this population, Diamond *et al.* demonstrated a 59% chance of having an abnormal total motile sperm count.²⁵⁸ Others have suggested that patients at all Tanner stages with an initial peak retrograde flow of greater than 38 cm/second coupled with a 20% testicular asymmetry had persistent or progressive hypotrophy over time.²⁶²

Additional indications for surgery are:

- bilateral grade 3 varicoceles,
- varicocele in a solitary testicle,
- a soft testis,

- poor semen analysis in a patient with Tanner stage 5, or
- pain/discomfort secondary to the varicocele.

Grade alone is not an indication for surgery.²⁶³

9.7.3.5 **Treatment options for adolescent varicocele**

Technique selection remains the subject of debate—the major issues are the level of venous ligation and preservation (or not) of the testicular artery.

The level at which venous flow is interrupted can be supra-inguinal, inguinal, or sub-inguinal. The advantage of the supra-inguinal approach lies in the fact that the venous drainage is managed after the pampiniform plexus has coalesced to the primary vein. This can be achieved using either endo-vascular embolization or a surgical approach.²⁶⁴ Regardless of how this is undertaken, this approach does not allow for disruption of the periarterial venous network or the external spermatic veins—two tributaries that may be responsible for varicocele recurrence.²⁶⁵ Both inguinal and sub-inguinal approaches allow for management of all of these venous tributaries.

The level of magnification used during the procedure correlates with surgical success. In one series comparing microsurgical magnification with loupe magnification with no magnification, post-oper-ative recurrences were noted in 0%, 2.9%, and 8.8%, respectively.²⁶⁶

Mass ligation (including the spermatic artery), as described by Palomo and later in laparoscopic approaches, has been shown to be better (with improved catch-up growth) than venous ligation alone. Consideration must be given to prior inguinal surgery (e.g., hernia repair or orchiopexy), then division of the testicular artery is not advised, as vasal blood supply could have been altered. Disruption of the testicular artery would preclude later use of vasectomy as a viable birth control method, as testicular atrophy may result.²⁶⁵

9.7.3.6 **Results of Intervention**

Varicocelectomy has been shown to improve testicular volume in the majority of patients.^{267,268} Varicocele repair can not only significantly improve semen parameters, but may also have a positive effect on Leydig cell function.^{266,268,269} However, despite these quantitative improvements, little to no data exists regarding the effect on paternity.

Radiologic embolization or sclerotherapy of spermatic veins is minimally invasive. However, it has a failure rate of up to 15%, and needs sufficient skill and experience. The high retroperitoneal (Palomo) and laparoscopic approaches can be used for internal spermatic vein ligation.^{264,270}

The inguinal (Ivanissevich) and sub-inguinal approaches can be also used to ligate the external spermatic veins.^{266,270,271} The use of microscopic magnification allows identification of the testicular artery, lymphatics, and small venous channels, giving a significant decrease in the incidence of hydrocele formation, testicular artery injury, and varicocele recurrence (LOE 3).^{271,272}

9.7.3.7 **Complications after varicocele repair**

Post-operative complications vary with surgical techniques. Recurrences after varicocele repair are reported in 0–16.6%. Hydrocele has an incidence of 0–24%. Both are reduced with a microsurgical approach (LOE 4).^{264,270,271,273,274}

Other complications include wound infection, testicular atrophy, and ilio-inguinal nerve damage, but the incidence is unrecorded. Testicular atrophy would be a devastating complication, but is not widely reported. Surgeons would be wise to warn of the remote possibility when obtaining consent.

9.7.3.8 **Post-operative results**

Varicocele repair has resulted in a significant increase in testicular volumes and consistency, and testicular catch-up growth has been found in 53–90% of adolescents.^{259,266,268,270,275} It is noteworthy that when follow-up into adulthood has been possible, the total testicular mass (that is the volume of both testes added together), has been the same in operated patients and normal controls and significantly larger than in men newly presenting with varicocele in adulthood.²⁵⁹

Studies suggest that varicocele repair in older adolescents significantly increases sperm parameters, especially motility and total motile sperm count (19;20;32). Repair probably has positive effects on Leydig cell function by improving serum testosterone level.^{251,266,276}

Evidence that paternity is affected is limited. It has been shown that operated patients are fertile, but there were no controls in the series, and so the fate of unoperated patients is not known.²⁷⁷ It is striking that even studies with long-term follow-up make little or no mention of paternity.

A meta-analysis showed improvement in sperm concentration, motility, and morphology in a half of the 12 studies. Varicocele grade was not predictive of fertility. Only 20% of adults with varicocele have any symptoms (including infertility).²⁷⁸ Data remain inconclusive.

9.7.3.9 **Recommendations**

Physical examination is sufficient to diagnose adolescent varicoceles (GOR A). Additional radiologic imaging is not necessary to diagnose subclinical varicocele in adolescents (GOR B).

Testicular volumes may be measured with an orchidometer or scrotal ultrasonography (GOR B). Testicular-scrotal ultrasound is a reliable method for serial follow-up of testicular size. Testicular size discrepancy of more than 2 mL or more than 20% difference on the affected side is considered diagnostic of testicular hypotrophy (GOR B).

Studies support the use of microscope magnification for varicocele surgery, (including lymphatic preservation) to reduce recurrence and other complications (GOR C).

Indications for varicocelectomy are a testicular size discrepancy of greater than or equal to 20%. Bilateral Grade 3 varicoceles, varicocele in a solitary testis, a soft testis, poor semen analysis in a patient with Tanner stage 5, or pain/discomfort is additional indication. Patients should be counseled that there is no definitive evidence for improved fertility following varicocelectomy.

Asynchronous testicular growth may resolve over time (so-called catch-up growth) with no intervention. It is thus recommended that at least two and preferably three serial ultrasounds be obtained at one-year intervals before a conclusion can be made as to the effect of the varicocele on testicular growth.

Mass ligation of the internal spermatic artery and vein are not recommended when the patient has had a prior inguinal procedure (orchiopexy or hernia-hydrocele repair) due to concerns that the prior procedure may have altered vasal blood supply.

If ligation of the artery is performed along with the vein (laparoscopic or open Palomo technique), then vasectomy is not advised as a future form of birth control.



9.8 **References**

- 1. Tanner, J.M., Growth at Adolescence. Oxford: Blackwell Scientific Publications, 1962.
- 2. Wilson, C.J., et al., The psychosocial impact of bladder exstrophy in adolescence. J Adolesc Health, 2007. 41(5):504-8.
- 3. Wilson, C., D. Christie, and C.R. Woodhouse, *The ambitions of adolescents born with exstrophy: a structured survey.* BJU Int, 2004. 94(4):607-12; discussion 612.
- 4. Avellan, L., *The development of puberty, the sexual debut and sexual function in hypospadiacs.* Scand J Plast Reconstr Surg, 1976. 10(1):29-44.
- Svensson, J., R. Berg, and G. Berg, Operated hypospadiacs: late follow-up. Social, sexual, and psychological adaptation. J Pediatr Surg, 1981. 16(2):134-5.
- Aho, M.O., et al., Sexual and social life of men operated in childhood for hypospadias and phimosis. A comparative study. Eur Urol, 2000. 37(1):95-100; discussion 101.
- 7. Bracka, A., A long-term view of hypospadias. Br J Plast Surg, 1989. 42(3):251-5.
- 8. Jones, B.C., et al., Early hypospadias surgery may lead to a better long-term psychosexual outcome. J Urol, 2009. 182(4 Suppl):1744-9.
- Hoag, C.C., et al., Long-term functional outcome and satisfaction of patients with hypospadias repaired in childhood. Can Urol Assoc J, 2008. 2(1):23-31.
- Mondaini, N., et al., Hypospadias: incidence and effects on psychosexual development as evaluated with the Minnesota Multiphasic Personality Inventory test in a sample of 11,649 young Italian men. Urol Int, 2002. 68(2):81-5.
- Jiao, C., et al., Long-term outcome of penile appearance and sexual function after hypospadias repairs: situation and relation. Int Urol Nephrol, 2011. 43(1):47-54.
- Moriya, K., et al., Long-term cosmetic and sexual outcome of hypospadias surgery: norm related study in adolescence. J Urol, 2006. 176(4 Pt 2):1889-92; discussion 1892-3.
- 13. Weber, D.M., et al., The Pediatric Penile Perception Score: an instrument for patient self-assessment and surgeon evaluation after hypospadias repair. J Urol, 2008. 180(3):1080-4; discussion 1084.
- van der Toorn, F., et al., Introducing the HOPE (Hypospadias Objective Penile Evaluation)-score: A validation study of an objective scoring system for evaluating cosmetic appearance in hypospadias patients. J Pediatr Urol, 2013.
- 15. Holland, A.J., *et al.*, HOSE: an objective scoring system for evaluating the results of hypospadias surgery. BJU Int, 2001. 88(3):255-8.
- 16. Sommerlad, B.C., A long-term follow-up of hypospadias patients. Br J Plast Surg, 1975. 28(4):324-30.
- 17. Van der Werff JF, U.J., Long-term follow up of hypospadias repair. . Br J Plast Surg 2000, 2000. 53(7):588-592
- 18. Aulagne, M.B., et al., Long-term outcome of severe hypospadias. J Pediatr Urol, 2010. 6(5):469-72.
- 19. Kumar, M.V. and D.L. Harris, Balanitis xerotica obliterans complicating hypospadias repair. Br J Plast Surg, 1999. 52(1):69-71.
- Lam, P.N., S.P. Greenfield, and P. Williot, 2-stage repair in infancy for severe hypospadias with chordee: long-term results after puberty. J Urol, 2005. 174(4 Pt 2):1567-72; discussion 1572.
- Robinson, A.J., L.E. Harry, and J.H. Stevenson, Assessment of long term function following hypospadias reconstruction: do flow rates, flow quality and cosmesis improve with time? Results from the modified Bretteville technique. J Plast Reconstr Aesthet Surg, 2013. 66(1):120-5.
- Moriya, K., et al., Long-term patient reported outcome of urinary symptoms after hypospadias surgery: norm related study in adolescents. J Urol, 2007. 178(4 Pt 2):1659-62; discussion 1662.
- Rynja, S.P., et al., Functional, cosmetic and psychosexual results in adult men who underwent hypospadias correction in childhood. J Pediatr Urol, 2011. 7(5):504-15.

- Ozkurkcugil, C., B.H. Guvenc, and O. Dillioglugil, First report of overactive detrusor in association with hypospadias detected by urodynamic screening. Neurourol Urodyn, 2005. 24(1):77-80.
- 25. Kaya, C., *et al.*, Value of urinary flow patterns in the follow-up of children who underwent Snodgrass operation. Urol Int, 2007. 78(3):245-8.
- Orkiszewski, M. and J. Leszniewski, Morphology and urodynamics after longitudinal urethral plate incision in proximal hypospadias repairs: long-term results. Eur J Pediatr Surg, 2004. 14(1):35-8.
- Perera, M., et al., Long-term urethral function measured by uroflowmetry after hypospadias surgery: comparison with an age matched control. J Urol, 2012. 188(4 Suppl):1457-62.
- 28. Kiss, A., et al., Long-term psychological and sexual outcomes of severe penile hypospadias repair. J Sex Med, 2011. 8(5):1529-39.
- Vandersteen, D.R. and D.A. Husmann, Late onset recurrent penile chordee after successful correction at hypospadias repair. J Urol, 1998. 160(3 Pt 2):1131-3; discussion 1137.
- 30. Flynn, J.T., S.R. Johnston, and J.P. Blandy, Late sequelae of hypospadias repair. Br J Urol, 1980. 52(6):555-9.
- 31. Yucel, S., *et al.*, Midline dorsal plication to repair recurrent chordee at reoperation for hypospadias surgery complication. J Urol, 2006. 175(2):699-702; discussion 702-3.
- 32. Bubanj, T.B., *et al.*, Sexual behavior and sexual function of adults after hypospadias surgery: a comparative study. J Urol, 2004. 171(5):1876-9.
- Aho, M.O., O.K. Tammela, and T.L. Tammela, Aspects of adult satisfaction with the result of surgery for hypospadias performed in childhood. Eur Urol, 1997. 32(2):218-22.
- Iwatsuki, S., et al., Endocrine assessment of prepubertal boys with a history of cryptorchidism and/or hypospadias: a pilot study. J Urol, 2011. 185(6 Suppl):2444-50.
- 35. Gearhart, J.P., et al., Endocrine evaluation of adults with mild hypospadias. J Urol, 1990. 144(2 Pt 1):274-7.
- Moriya, K., et al., Long-term outcome of pituitary-gonadal axis and gonadal growth in patients with hypospadias at puberty. J Urol, 2010. 184(4 Suppl):1610-4.
- 37. Hensle, T.W., et al., Hypospadias repair in adults: adventures and misadventures. J Urol, 2001. 165(1):77-9.
- Ching, C.B., et al., The Cleveland Clinic experience with adult hypospadias patients undergoing repair: their presentation and a new classification system. BJU Int, 2011. 107(7):1142-6.
- Hensle, T.W., M.C. Kearney, and J.B. Bingham, Buccal mucosa grafts for hypospadias surgery: long-term results. J Urol, 2002. 168(4 Pt 2):1734-6; discussion 1736-7.
- 40. Adayener, C. and I. Akyol, Distal hypospadias repair in adults: the results of 97 cases. Urol Int, 2006. 76(3):247-51.
- 41. Dodson, J.L., et al., Outcomes of delayed hypospadias repair: implications for decision making. J Urol, 2007. 178(1):278-81.
- 42. Kocherov, S., et al., Outcome of hypospadias repair in toilet-trained children and adolescents. Pediatr Surg Int, 2012. 28(4):429-33.
- 43. Senkul, T., et al., Hypospadias in adults. Urology, 2002. 60(6):1059-62.
- 44. Secrest, C.L., et al., Repair of the complications of hypospadias surgery. J Urol, 1993. 150(5 Pt 1):1415-8.
- 45. Bracka, A., Hypospadias repair: the two-stage alternative. Br J Urol, 1995. 76 Suppl 3:31-41.
- 46. Sharma, G., Tubularized-incised plate urethroplasty in adults. BJU Int, 2005. 95(3):374-6.
- 47. Snodgrass, W.T. and A. Lorenzo, Tubularized incised-plate urethroplasty for proximal hypospadias. BJU Int, 2002. 89(1):90-3.
- 48. Spinoit, A.F., *et al.*, Hypospadias repair at a tertiary care center: long-term followup is mandatory to determine the real complication rate. J Urol, 2013. 189(6):2276-81.
- 49. van der Werff, J.F. and J.C. van der Meulen, Treatment modalities for hypospadias cripples. Plast Reconstr Surg, 2000. 105(2):600-8.
- 50. Nuininga, J.E., *et al.*, Long-term outcome of different types of 1-stage hypospadias repair. J Urol, 2005. 174(4 Pt 2):1544-8; discussion 1548.

- 51. Scherz, H.C., et al., Urethral strictures after hypospadias repair. J Urol (Paris), 1989. 95(1):23-6.
- 52. Burger, R.A., et al., The buccal mucosal graft for urethral reconstruction: a preliminary report. J Urol, 1992. 147(3):662-4.
- 53. Castagnetti, M., *et al.*, Long-term (>5 years) donor site outcome after mandibular labial mucosa graft harvesting for urethral reconstruction in children. J Pediatr Urol, 2008. 4(6):442-4.
- 54. Goyal, A., M.V. Singh, and A.P. Dickson, Oral mucosa graft for repair of hypospadias: outcomes at puberty. J Urol, 2010. 184(6):2504-8.
- 55. Zhao, M., et al., Two-stage repair with buccal mucosa for severe and complicated hypospadias in adults. Int J Urol, 2011. 18(2):155-61.
- 56. Ye, W.J., *et al.*, Single stage dorsal inlay buccal mucosal graft with tubularized incised urethral plate technique for hypospadias reoperations. Asian J Androl, 2008. 10(4):682-6.
- Mokhless, I.A., et al., The multistage use of buccal mucosa grafts for complex hypospadias: histological changes. J Urol, 2007. 177(4):1496-9; discussion 1499-500.
- 58. Sahin, C. and T. Seyhan, Use of buccal mucosal grafts in hypospadia-crippled adult patients. Ann Plast Surg, 2003. 50(4):382-6.
- Snodgrass, W. and J. Elmore, Initial experience with staged buccal graft (Bracka) hypospadias reoperations. J Urol, 2004. 172(4 Pt 2):1720-4; discussion 1724.
- Fichtner, J., et al., Long-term followup of buccal mucosa onlay graft for hypospadias repair: analysis of complications. J Urol, 2004. 172(5 Pt 1):1970-2; discussion 1972.
- 61. Barbagli, G., et al., Failed hypospadias repair presenting in adults. Eur Urol, 2006. 49(5):887-94; discussion 895.
- Meeks, J.J., B.A. Erickson, and C.M. Gonzalez, Staged reconstruction of long segment urethral strictures in men with previous pediatric hypospadias repair. J Urol, 2009. 181(2):685-9.
- Nelson, C.P., et al., Long-term patient reported outcome and satisfaction after oral mucosa graft urethroplasty for hypospadias. J Urol, 2005. 174(3):1075-8.
- 64. Nelson, C.P., et al., Patient-reported sexual function after oral mucosa graft urethroplasty for hypospadias. Urology, 2005. 66(5):1086-9; discussion 1089-90.
- 65. Berg R, B.G., Svensson J., Penile malformation and mental health: A controlled psychiatric study of men operated for hypospadias in childhood. Acta psychiat scand 1982. 66:398-416
- Wang, W.W., et al., Psychosexual adjustment and age factors in 130 men undergone hypospadias surgery in a Chinese hospital. Andrologia, 2010. 42(6):384-8.
- Wang, W.W., et al., Long-term sexual activity status and influencing factors in men after surgery for hypospadias. Asian J Androl, 2009. 11(4):417-22.
- Mureau, M.A., et al., Psychosocial functioning of children, adolescents, and adults following hypospadias surgery: a comparative study. J Pediatr Psychol, 1997. 22(3):371-87.
- 69. Vandendriessche, S., et al., Body image and sexuality in adolescents after hypospadias surgery. J Pediatr Urol, 2010. 6(1):54-9.
- Mureau, M.A., et al., Psychosexual adjustment of children and adolescents after different types of hypospadias surgery: a normrelated study. J Urol, 1995. 154(5):1902-7.
- Mureau, M.A., *et al.*, Satisfaction with penile appearance after hypospadias surgery: the patient and surgeon view. J Urol, 1996. 155(2):703-6.
- 72. Schonbucher, V.B., et al., Psychosexual development of children and adolescents with hypospadias. J Sex Med, 2008. 5(6):1365-73.
- Schonbucher, V.B., et al., Health-related quality of life and psychological adjustment of children and adolescents with hypospadias. J Pediatr, 2008. 152(6):865-72.
- 74. Ekmark, A.N., et al., Postpubertal examination after hypospadias repair is necessary to evaluate the success of the primary reconstruction. Eur J Pediatr Surg, 2013. 23(4):304-11.
- 75. Asklund, C., *et al.*, Semen quality, reproductive hormones and fertility of men operated for hypospadias. Int J Androl, 2010. 33(1):80-7.

- 76. Woodhouse, C.R.J., Reconstruction of the penis in men born with epispadias and exstrophy. European Journal of Plastic Surgery, 2005. 28:70.
- 77. Jarzebowski, A.C., et al., The Kelly technique of bladder exstrophy repair: continence, cosmesis and pelvic organ prolapse outcomes. J Urol, 2009. 182(4 Suppl):1802-6.
- 78. Woodhouse, C.R. and M.J. Kellett, Anatomy of the penis and its deformities in exstrophy and epispadias. J Urol, 1984. 132(6):1122-4.
- Cervellione, R.M., et al., Penile ischemic injury in the exstrophy/epispadias spectrum: new insights and possible mechanisms. J Pediatr Urol, 2010. 6(5):450-6.
- Snyder, H.M., Epispadias and exstrophy. In: Rob and Smith's Operative Surgery: Genito Urinary Surgery. Edited by Whitfield, H. N.: Oxford: Butterworth-Heinemann., 1993. 5th ed.:p786.
- 81. Perovic, S., et al., Epispadias surgery--Belgrade experience. Br J Urol, 1992. 70(6):674-7.
- 82. Castagnetti, M., *et al.*, Sexual function in men born with classic bladder exstrophy: a norm related study. J Urol, 2010. 183(3):1118-22.
- 83. Hanna, M.K. and D.I. Williams, Genital function in males with vesical exstrophy and epispadias. Br J Urol, 1972. 44(2):169-74.
- Mesrobian, H.G., P.P. Kelalis, and S.A. Kramer, Long-term followup of cosmetic appearance and genital function in boys with exstrophy: review of 53 patients. J Urol, 1986. 136(1 Pt 2):256-8.
- 85. Silver, R.I., et al., Penile length in adulthood after exstrophy reconstruction. J Urol, 1997. 157(3):999-1003.
- Gobet, R., et al., Long-term follow up (37-69 years) of patients with bladder exstrophy treated with ureterosigmoidostomy: uro-nephrological outcome. J Pediatr Urol, 2009. 5(3):190-6.
- 87. Woodhouse, C.R., Sexual function in boys born with exstrophy, myelomeningocele, and micropenis. Urology, 1998. 52(1):3-11.
- Pennison, M.C., et al., A survey to assess body and self-image in individuals with bladder exstrophy: a call for psychosocial support. J Urol, 2013. 190(4 Suppl):1572-6.
- 89. Ben-Chaim, J., et al., The outcome of patients with classic bladder exstrophy in adult life. J Urol, 1996. 155(4):1251-2.
- De Fontaine, S., et al., Complete phalloplasty using the free radial forearm flap for correcting micropenis associated with vesical exstrophy. J Urol, 2001. 166(2):597-9.
- Massanyi, E.Z., et al., Radial forearm free flap phalloplasty for penile inadequacy in patients with exstrophy. J Urol, 2013. 190(4 Suppl):1577-82.
- 92. Timsit, M.O., et al., Use of forearm free-flap phalloplasty in bladder exstrophy adults. BJU Int, 2009. 103(10):1418-21.
- Lumen, N., et al., Phalloplasty: a valuable treatment for males with penile insufficiency. Urology, 2008. 71(2):272-6; discussion 276-7.
- Merksz, M. and J. Toth, The state of the testicle and the epididymis associated with exstrophy of the bladder in undescended testes. Acta Chir Hung, 1990. 31(4):297-301.
- Ebert, A.K., et al., Genital and reproductive function in males after functional reconstruction of the exstrophy-epispadias complex--long-term results. Urology, 2008. 72(3):566-9; discussion 569-70.
- 96. Woodhouse, C.R., Prospects for fertility in patients born with genitourinary anomalies. J Urol, 2001. 165(6 Pt 2):2354-60.
- D'Hauwers, K.W., W.F. Feitz, and J.A. Kremer, Bladder exstrophy and male fertility: pregnancies after ICSI with ejaculated or epididymal sperm. Fertil Steril, 2008. 89(2):387-9.
- Stec, A.A., et al., Pelvic floor anatomy in classic bladder exstrophy using 3-dimensional computerized tomography: initial insights. J Urol, 2001. 166(4):1444-9.
- Halachmi, S., et al., Pelvic floor magnetic resonance imaging after neonatal single stage reconstruction in male patients with classic bladder exstrophy. J Urol, 2003. 170(4 Pt 2):1505-9.
- 100. Anusionwu, I., et al., Comparison of musculoskeletal anatomic relationships, determined by magnetic resonance imaging, in postpubertal female patients with and without classic bladder exstrophy. BJU Int, 2013. 112(2):E195-200.
- 101. Anusionwu, I., *et al.*, Is pelvic osteotomy associated with lower risk of pelvic organ prolapse in postpubertal females with classic bladder exstrophy? J Urol, 2012. 188(6):2343-6.
- 102. Mathews, R.I., M. Gan, and J.P. Gearhart, Urogynaecological and obstetric issues in women with the exstrophy-epispadias complex. BJU Int, 2003. 91(9):845-9.
- 103. Kropp, B.P. and E.Y. Cheng, Total urogenital complex mobilization in female patients with exstrophy. J Urol, 2000. 164(3 Pt 2):1035-9.
- 104. Cervellione, R.M., *et al.*, Vaginoplasty in the female exstrophy population: Outcomes and complications. J Pediatr Urol, 2010. 6(6):595-9.
- 105. Cook, A.J., et al., Simplified mons plasty: a new technique to improve cosmesis in females with the exstrophy-epispadias complex. J Urol, 2005. 173(6):2117-20.
- Crouch, N.S., et al., Sexual function and genital sensitivity following feminizing genitoplasty for congenital adrenal hyperplasia. J Urol, 2008. 179(2):634-8.
- 107. Castagnetti, M., *et al.*, Issues with the external and internal genitalia in postpubertal females born with classic bladder exstrophy: a surgical series. J Pediatr Adolesc Gynecol, 2011. 24(1):48-52.
- VanderBrink, B.A., J.A. Stock, and M.K. Hanna, Aesthetic aspects of reconstructive clitoroplasty in females with bladder exstrophy-epispadias complex. J Plast Reconstr Aesthet Surg, 2010. 63(12):2141-5.
- 109. Woodhouse, C.R., The gynaecology of exstrophy. BJU Int, 1999. 83 Suppl 3:34-8.
- 110. Nakhal, R.S., et al., Genital prolapse in adult women with classical bladder exstrophy. Int Urogynecol J, 2012.
- 111. Stein, R., *et al.*, Operative reconstruction of the external and internal genitalia in female patients with bladder exstrophy or incontinent epispadias. J Urol, 1995. 154(3):1002-7.
- 112. Stein, R., et al., The fate of the adult exstrophy patient. J Urol, 1994. 152(5 Pt 1):1413-6.
- 113. Burbige, K.A., et al., Pregnancy and sexual function in women with bladder exstrophy. Urology, 1986. 28(1):12-4.
- 114. Deans, R., *et al.*, Reproductive outcomes in women with classic bladder exstrophy: an observational cross-sectional study. Am J Obstet Gynecol, 2012. 206(6):496 e1-6.
- 115. Greenwell, T.J., et al., Pregnancy after lower urinary tract reconstruction for congenital abnormalities. BJU Int, 2003. 92(7):773-7.
- 116. Woodhouse, C.R., The sexual and reproductive consequences of congenital genitourinary anomalies. J Urol, 1994. 152(2 Pt 2):645-51.
- 117. Thomas, J.C. and M.C. Adams, Female sexual function and pregnancy after genitourinary reconstruction. J Urol, 2009. 182(6):2578-84.
- Pena, A., The surgical management of persistent cloaca: results in 54 patients treated with a posterior sagittal approach. J Pediatr Surg, 1989. 24(6):590-8.
- 119. Hendren, W.H., Cloaca, the most severe degree of imperforate anus: experience with 195 cases. Ann Surg, 1998. 228(3):331-46.
- Sheldon, C.A., DeFoor, W.R., Anorectal malformation and cloaca. 5th ed. Textbook of Clinical Pediatric Urology, ed. P.P. Kelalis, King, L.R., Belman, A.B.2007: WB Saunders.
- 121. Warne, S.A., et al., Renal outcome in patients with cloaca. J Urol, 2002. 167(6):2548-51; discussion 2551.
- 122. Levitt, M.A. and A. Pena, Cloacal malformations: lessons learned from 490 cases. Semin Pediatr Surg, 2010. 19(2):128-38.
- Warne, S.A., D.T. Wilcox, and P.G. Ransley, Long-term urological outcome of patients presenting with persistent cloaca. J Urol, 2002. 168(4 Pt 2):1859-62; discussion 1862.
- 124. Warne, S.A., M.L. Godley, and D.T. Wilcox, Surgical reconstruction of cloacal malformation can alter bladder function: a comparative study with anorectal anomalies. J Urol, 2004. 172(6 Pt 1):2377-81; discussion 2381.
- 125. Qi, B.Q., et al., Clarification of the process of separation of the cloaca into rectum and urogenital sinus in the rat embryo. J Pediatr Surg, 2000. 35(12):1810-6.

- 126. Pena, A., et al., Surgical management of cloacal malformations: a review of 339 patients. J Pediatr Surg, 2004. 39(3):470-9; discussion 470-9.
- 127. Pena, A., *et al.*, Posterior cloaca--further experience and guidelines for the treatment of an unusual anorectal malformation. J Pediatr Surg, 2010. 45(6):1234-40.
- 128. Rink, R.C., *et al.*, Upper and lower urinary tract outcome after surgical repair of cloacal malformations: a three-decade experience. BJU Int, 2005. 96(1):131-4.
- 129. Breech, L., Gynecologic concerns in patients with anorectal malformations. Semin Pediatr Surg, 2010. 19(2):139-45.
- 130. Warne, S.A., et al., Long-term gynecological outcome of patients with persistent cloaca. J Urol, 2003. 170(4 Pt 2):1493-6.
- 131. Bischoff, A., et al., Hydrocolpos in cloacal malformations. J Pediatr Surg, 2010. 45(6):1241-5.
- 132. Levitt, M.A., D.M. Stein, and A. Pena, Gynecologic concerns in the treatment of teenagers with cloaca. J Pediatr Surg, 1998. 33(2):188-93.
- 133. Hendren, W.H., Further experience in reconstructive surgery for cloacal anomalies. J Pediatr Surg, 1982. 17(6):695-717.
- 134. Pena, A., Posterior sagittal approach for the correction of anorectal malformations. Adv Surg, 1986. 19:69-100.
- 135. Pena, A., Total urogenital mobilization--an easier way to repair cloacas. J Pediatr Surg, 1997. 32(2):263-7; discussion 267-8.
- 136. Leclair, M.D., et al., The surgical outcome of total urogenital mobilization for cloacal repair. J Urol, 2007. 177(4):1492-5.
- 137. Rink, R.C. and M.P. Cain, Urogenital mobilization for urogenital sinus repair. BJU Int, 2008. 102(9):1182-97.
- 138. Bischoff, A., M.A. Levitt, and A. Pena, Laparoscopy and its use in the repair of anorectal malformations. J Pediatr Surg, 2011. 46(8):1609-17.
- 139. Alizai, N.K., *et al.*, Feminizing genitoplasty for congenital adrenal hyperplasia: what happens at puberty? J Urol, 1999. 161(5):1588-91.
- 140. L, H.L.H.J.P.L.M.B., Bowel vaginoplasty associated with complex anorectal malformations: A retrospective review of 131 cases. North American Society for Pediatric & Adolescent Gynecology Annual Clinical Meeting April 23-25, San Antonio, TX. Professional Meeting. National, 2009.
- 141. Schober, J.M., Cancer of the neovagina. J Pediatr Urol, 2007. 3(3):167-70.
- 142. Oakes, M.B., *et al.*, Augmentation vaginoplasty of colonic neovagina stricture using oral mucosa graft. J Pediatr Adolesc Gynecol, 2010. 23(1):e39-42.
- 143. Samuelson, M.L. and L.A. Baker, Autologous buccal mucosa vulvovaginoplasty for high urogenital sinus. J Pediatr Urol, 2006. 2(5):486-8.
- 144. Warne, S.A., et al., Understanding cloacal anomalies. Arch Dis Child, 2011. 96(11):1072-6.
- Mollitt, D.L., *et al.*, Complications at menarche of urogenital sinus with associated anorectal malformations. J Pediatr Surg, 1981. 16(3):349-52.
- 146. Greenberg, J.A., et al., Triplets after cloacal malformation repair. J Pediatr Adolesc Gynecol, 2003. 16(1):43-4.
- 147. Hughes, I.A., et al., Consensus statement on management of intersex disorders. Arch Dis Child, 2006. 91(7):554-63.
- 148. Warne, G., Support groups for CAH and AIS. The Endocrinologist, 2003. 13:175-178.
- 149. Diamond, M., Pediatric management of ambiguous and traumatized genitalia. J Urol, 1999. 162(3 Pt 2):1021-8.
- 150. Rink, R.C. and M.C. Adams, Feminizing genitoplasty: state of the art. World J Urol, 1998. 16(3):212-8.
- 151. Davies, M.C., S.M. Creighton, and C.R. Woodhouse, The pitfalls of vaginal construction. BJU Int, 2005. 95(9):1293-8.
- 152. Baskin, L.S., et al., Anatomical studies of the human clitoris. J Urol, 1999. 162(3 Pt 2):1015-20.
- 153. O'Connell, H.E., K.V. Sanjeevan, and J.M. Hutson, Anatomy of the clitoris. J Urol, 2005. 174(4 Pt 1):1189-95.
- 154. Rajimwale, A., et al., Vaginal construction using sigmoid colon in children and young adults. BJU Int, 2004. 94(1):115-9.

- Crouch, N.S., et al., Genital sensation after feminizing genitoplasty for congenital adrenal hyperplasia: a pilot study. BJU Int, 2004. 93(1):135-8.
- 156. Hensle, T.W., et al., Sexual function following bowel vaginoplasty. J Urol, 2006. 175(6):2283-6.
- Woodhouse, C.R.J., The consequences of intersex conditions in adult life. Principles of gender specific medicine. San Diego: Elsevier Academic Press, 2004.; 2004. In: Legato MJ, editor:615-625.
- 158. Jarolim, L., Surgical conversion of genitalia in transsexual patients. BJU Int, 2000. 85(7):851-6.
- 159. Tillem, S.M., J.A. Stock, and M.K. Hanna, Vaginal construction in children. J Urol, 1998. 160(1):186-90.
- Passerini-Glazel, G., A new 1-stage procedure for clitorovaginoplasty in severely masculinized female pseudohermaphrodites. J Urol, 1989. 142(2 Pt 2):565-8; discussion 572.
- 161. Rink, R.C., et al., Partial urogenital mobilization: a limited proximal dissection. J Pediatr Urol, 2006. 2(4):351-6.
- 162. Domini, R., *et al.*, Anterior sagittal transanorectal approach to the urogenital sinus in adrenogenital syndrome: preliminary report. J Pediatr Surg, 1997. 32(5):714-6.
- 163. Frank, R., The formation of an artifical vagina without an operation. Am J OG, 1938. 35:1053-1055.
- 164. Steiner, E., et al., Carcinoma of the neovagina: case report and review of the literature. Gynecol Oncol, 2002. 84(1):171-5.
- Ismail, I.S., A.S. Cutner, and S.M. Creighton, Laparoscopic vaginoplasty: alternative techniques in vaginal reconstruction. BJOG, 2006. 113(3):340-3.
- El Saman, A.M., et al., Enhancement balloon vaginoplasty for treatment of blind vagina due to androgen insensitivity syndrome. Fertil Steril, 2011. 95(2):779-82.
- Bannister JB, M.A., Congenital absence of the vagina, treated by means of an indwelling skin-graft. Proceedings of the Royal Society of Medicine, 1938. 31:1055-1056.
- 168. Giannesi, A., et al., Sexuality after laparoscopic Davydov in patients affected by congenital complete vaginal agenesis associated with uterine agenesis or hypoplasia. Hum Reprod, 2005. 20(10):2954-7.
- 169. Davies, M.C., et al., Congenital adrenal hyperplasia and lower urinary tract symptoms. BJU Int, 2005. 95(9):1263-6.
- 170. Mouriquand, P.D. and P.Y. Mure, Current concepts in hypospadiology. BJU Int, 2004. 93 Suppl 3:26-34.
- 171. Perovic, S., Phalloplasty in children and adolescents using the extended pedicle island groin flap. J Urol, 1995. 154(2 Pt 2):848-53.
- Mathews, R., et al., Tissue expansion in management of failed phallic reconstruction: initial report of clinical series. Urology, 2005. 66(1):180-4.
- 173. Kwon, T.G., J.J. Yoo, and A. Atala, Autologous penile corpora cavernosa replacement using tissue engineering techniques. J Urol, 2002. 168(4 Pt 2):1754-8.
- 174. Reilly, J.M. and C.R. Woodhouse, Small penis and the male sexual role. J Urol, 1989. 142(2 Pt 2):569-71; discussion 572.
- 175. Berkowitz, G.S., et al., Prevalence and natural history of cryptorchidism. Pediatrics, 1993. 92(1):44-9.
- 176. Scorer, C.G., The Descent of the Testis. Arch Dis Child, 1964. 39:605-9.
- 177. Giannopoulos, M.F., I.G. Vlachakis, and G.C. Charissis, 13 Years' experience with the combined hormonal therapy of cryptorchidism. Horm Res, 2001. 55(1):33-7.
- Schneck FX, B.M., Abnormalities of the testes and scrotum and their surgical management. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's Urology. Philadelphia: WBSaunders, , 2002:2353-2394.
- 179. Taran, I. and J.S. Elder, Results of orchiopexy for the undescended testis. World J Urol, 2006. 24(3):231-9.
- 180. Batata, M.A., et al., Cryptorchidism and testicular cancer. J Urol, 1980. 124(3):382-7.
- Hrebinko, R.L. and M.F. Bellinger, The limited role of imaging techniques in managing children with undescended testes. J Urol, 1993. 150(2 Pt 1):458-60.
- 182. Davenport, M., *et al.*, The use of the hCG stimulation test in the endocrine evaluation of cryptorchidism. Br J Urol, 1995. 76(6):790-4.

- Kolon, T.F., R.P. Patel, and D.S. Huff, Cryptorchidism: diagnosis, treatment, and long-term prognosis. Urol Clin North Am, 2004. 31(3):469-80, viii-ix.
- 184. Oh, J., et al., Management of the postpubertal patient with cryptorchidism: an updated analysis. J Urol, 2002. 167(3):1329-33.
- Fowler, R. and F.D. Stephens, The role of testicular vascular anatomy in the salvage of high undescended testes. Aust N Z J Surg, 1959. 29:92-106.
- PG., R., Preliminary ligation of the gonadal vessels prior to orchiopexy for the intra-abdominal testicle: a staged Fowler-Stephens procedure. . World J Urol, 1984. 2:266-270.
- 187. Harrison, C.B., *et al.*, Microvascular autotransplantation of the intra-abdominal testis. J Urol, 1990. 144(2 Pt 2):506-7; discussion 512-3.
- 188. Baker, L.A., et al., A multi-institutional analysis of laparoscopic orchidopexy. BJU Int, 2001. 87(6):484-9.
- 189. Wacksman, J., M. Dinner, and M. Handler, Results of testicular autotransplantation using the microvascular technique: experience with 8 intra-abdominal testes. J Urol, 1982. 128(6):1319-21.
- 190. Ford, T.F., M.C. Parkinson, and J.P. Pryor, The undescended testis in adult life. Br J Urol, 1985. 57(2):181-4.
- 191. Eldrup, J. and K. Steven, Influence of orchidopexy for cryptorchidism on subsequent fertility. Br J Surg, 1980. 67(4):269-70.
- 192. Alpert, P.F. and R.S. Klein, Spermatogenesis in the unilateral cryptorchid testis after orchiopexy. J Urol, 1983. 129(2):301-2.
- 193. Hadziselimovic, F., Cryptorchidism, its impact on male fertility. Eur Urol, 2002. 41(2):121-3.
- 194. Hadziselimovic, F. and B. Herzog, The importance of both an early orchidopexy and germ cell maturation for fertility. Lancet, 2001. 358(9288):1156-7.
- 195. Miller, K.D., M.T. Coughlin, and P.A. Lee, Fertility after unilateral cryptorchidism. Paternity, time to conception, pretreatment testicular location and size, hormone and sperm parameters. Horm Res, 2001. 55(5):249-53.
- 196. Lee, P.A., et al., Paternity after cryptorchidism: lack of correlation with age at orchidopexy. Br J Urol, 1995. 75(6):704-7.
- 197. Carpi, A., *et al.*, Spermatogenesis in azoospermic, formerly cryptorchid men. Use of needle aspiration techniques. Acta Cytol, 2002. 46(5):848-54.
- 198. Mollaeian, M., V. Mehrabi, and B. Elahi, Significance of epididymal and ductal anomalies associated with undescended testis: study in 652 cases. Urology, 1994. 43(6):857-60.
- 199. Agarwal, P.K., M. Diaz, and J.S. Elder, Retractile testis--is it really a normal variant? J Urol, 2006. 175(4):1496-9.
- Coughlin, M.T., M.F. Bellinger, and P.A. Lee, Age at unilateral orchiopexy: effect on hormone levels and sperm count in adulthood. J Urol, 1999. 162(3 Pt 2):986-8; discussion 989.
- 201. Lee, P.A. and M.T. Coughlin, Leydig cell function after cryptorchidism: evidence of the beneficial result of early surgery. J Urol, 2002. 167(4):1824-7.
- 202. Mirilas, P., C. Mamoulakis, and M. De Almeida, Puberty does not induce serum antisperm surface antibodies in patients with previously operated cryptorchidism. J Urol, 2003. 170(6 Pt 1):2432-5.
- 203. Giwercman, A., et al., Testicular cancer risk in boys with maldescended testis: a cohort study. J Urol, 1987. 138(5):1214-6.
- 204. Herrinton, L.J., W. Zhao, and G. Husson, Management of cryptorchism and risk of testicular cancer. Am J Epidemiol, 2003. 157(7):602-5.
- 205. Swerdlow, A.J., C.D. Higgins, and M.C. Pike, Risk of testicular cancer in cohort of boys with cryptorchidism. BMJ, 1997. 314(7093):1507-11.
- 206. Pottern, L.M., *et al.*, Testicular cancer risk among young men: role of cryptorchidism and inguinal hernia. J Natl Cancer Inst, 1985. 74(2):377-81.
- 207. Coughlin, M.T., et al., Testicular suture: a significant risk factor for infertility among formerly cryptorchid men. J Pediatr Surg, 1998. 33(12):1790-3.
- 208. Husmann, D.A., Cryptorchidism and its relationship to testicular neoplasia and microlithiasis. Urology, 2005. 66(2):424-6.
- 209. Cohen-Kettenis, P., Psychological long-term outcome in intersex conditions. Horm Res, 2005. 64 Suppl 2:27-30.

- Woodhouse, C.R.J., The gynaecology of the major genitourinary anomalies. In: Balen AH, editor. Paediatric and Adolescent Gynaecology - a Multidisiplinary Approach. Cambridge: Cambridge University Press., 2004:293-309.
- Katz, M.D., et al., Paternity by intrauterine insemination with sperm from a man with 5alpha-reductase-2 deficiency. N Engl J Med, 1997. 336(14):994-7.
- Nordenskjold, A. and S.A. Ivarsson, Molecular characterization of 5 alpha-reductase type 2 deficiency and fertility in a Swedish family. J Clin Endocrinol Metab, 1998. 83(9):3236-8.
- 213. Migeon, C.J., *et al.*, Ambiguous genitalia with perineoscrotal hypospadias in 46,XY individuals: long-term medical, surgical, and psychosexual outcome. Pediatrics, 2002. 110(3):e31.
- Cools, M., et al., Gonadal pathology and tumor risk in relation to clinical characteristics in patients with 45,X/46,XY mosaicism. J Clin Endocrinol Metab, 2011. 96(7):E1171-80.
- 215. Hurt, W.G., et al., Seminoma in pubertal patient with androgen insensitivity syndrome. Am J Obstet Gynecol, 1989. 161(3):530-1.
- 216. Hannema, S.E., et al., Testicular development in the complete androgen insensitivity syndrome. J Pathol, 2006. 208(4):518-27.
- Nakhal, R.S., et al., Evaluation of retained testes in adolescent girls and women with complete androgen insensitivity syndrome. Radiology, 2013. 268(1):153-60.
- Grumbach MM, H.I., Disorders of sex differentiation. In: Grumbach MM, Hughes IA, Conte FA, editors. Williams textbook of endocrinology. London: WBSaunders,, 2003:842-1002.
- 219. Rorth, M., et al., Carcinoma in situ in the testis. Scand J Urol Nephrol Suppl, 2000(205):166-86.
- 220. Nihoul-Fekete, C., *et al.*, Long-term surgical results and patient satisfaction with male pseudohermaphroditism or true hermaphroditism: a cohort of 63 patients. J Urol, 2006. 175(5):1878-84.
- Kitamura, M., et al., Ejaculated spermatozoa in patients with non-mosaic Klinefelter's syndrome. Int J Urol, 2000. 7(3):88-92; discussion 93-4.
- De Sanctis, V. and S. Ciccone, Fertility preservation in adolescents with Klinefelter's syndrome. Pediatr Endocrinol Rev, 2010. 8 Suppl 1:178-81.
- 223. Hughes, I.A., et al., Consensus statement on management of intersex disorders. J Pediatr Urol, 2006. 2(3):148-62.
- 224. Eroglu, E., et al., Buried penis after newborn circumcision. J Urol, 2009. 181(4):1841-3.
- 225. Shaeer, O. and K. Shaeer, Revealing the buried penis in adults. J Sex Med, 2009. 6(3):876-85.
- Perger, L., R.S. Hanley, and N.R. Feins, Penoplasty for buried penis in infants and children: report of 100 cases. Pediatr Surg Int, 2009. 25(2):175-80.
- Spyropoulos, E., I. Galanakis, and A. Dellis, Augmentation Phalloplasty Patient Selection and Satisfaction Inventory: a novel questionnaire to evaluate patients considered for augmentation phalloplasty surgery because of penile dysmorphophobia. Urology, 2007. 70(2):221-6.
- 228. Chu, C.C., et al., Preputial flaps to correct buried penis. Pediatr Surg Int, 2007. 23(11):1119-21.
- 229. Pestana, I.A., et al., Management of "buried" penis in adulthood: an overview. Plast Reconstr Surg, 2009. 124(4):1186-95.
- 230. Rogers, Z.R., Priapism in sickle cell disease. Hematol Oncol Clin North Am, 2005. 19(5):917-28, viii.
- Chinegwundoh, F. and K.A. Anie, Treatments for priapism in boys and men with sickle cell disease. Cochrane Database Syst Rev, 2004(4):CD004198.
- Rachid-Filho, D., et al., Treatment of recurrent priapism in sickle cell anemia with finasteride: a new approach. Urology, 2009. 74(5):1054-7.
- 233. Bialecki, E.S. and K.R. Bridges, Sildenafil relieves priapism in patients with sickle cell disease. Am J Med, 2002. 113(3):252.
- 234. Coull, N. and T. O'Brien, 'Street urology': beyond the formulary. BJU Int, 2009. 103(6):721-2.
- Rodriguez-Blaquez, H.M., P.E. Cardona, and J.L. Rivera-Herrera, Priapism associated with the use of topical cocaine. J Urol, 1990. 143(2):358.
- 236. Aoyagi, T., et al., Sildenafil induced priapism. Bull Tokyo Dent Coll, 1999. 40(4):215-7.

- 237. Kumar, R., L. Jindal, and A. Seth, Priapism following oral sildenafil abuse. Natl Med J India, 2005. 18(1):49.
- 238. Wills, B.K., et al., Sildenafil citrate ingestion and prolonged priapism and tachycardia in a pediatric patient. Clin Toxicol (Phila), 2007. 45(7):798-800.
- 239. Wilt, T.J. and H.A. Fink, Is antidepressant plus sildenafil a recipe for priapism? Postgrad Med, 2004. 116(6):11-2.
- 240. Ibrahiem el, H.I., et al., Penile fracture: long-term outcome of immediate surgical intervention. Urology, 2010. 75(1):108-11.
- 241. Nawaz, H., et al., Penile fracture: presentation and management. J Coll Physicians Surg Pak, 2010. 20(5):331-4.
- 242. Yapanoglu, T., *et al.*, Seventeen years' experience of penile fracture: conservative vs. surgical treatment. J Sex Med, 2009. 6(7):2058-63.
- 243. Waxman, S., et al., Penetrating trauma to the external genitalia in Operation Iraqi Freedom. Int J Impot Res, 2009. 21(2):145-8.
- 244. Skoog, S.J., et al., The adolescent varicocele: what's new with an old problem in young patients? Pediatrics, 1997. 100(1):112-21.
- Wishahi, M.M., Anatomy of the spermatic venous plexus (pampiniform plexus) in men with and without varicocele: intraoperative venographic study. J Urol, 1992. 147(5):1285-9.
- 246. lafrate, M., et al., Varicocele is associated with an increase of connective tissue of the pampiniform plexus vein wall. World J Urol, 2009. 27(3):363-9.
- 247. Shafik, A., et al., Testicular veins: anatomy and role in varicocelogenesis and other pathologic conditions. Urology, 1990. 35(2):175-82.
- 248. Cayan, S., *et al.*, Diagnosis of pediatric varicoceles by physical examination and ultrasonography and measurement of the testicular volume: using the prader orchidometer versus ultrasonography. Urol Int, 2002. 69(4):293-6.
- 249. Diamond, D.A., *et al.*, Comparative assessment of pediatric testicular volume: orchidometer versus ultrasound. J Urol, 2000. 164(3 Pt 2):1111-4.
- Chipkevitch, E., et al., Clinical measurement of testicular volume in adolescents: comparison of the reliability of 5 methods. J Urol, 1996. 156(6):2050-3.
- 251. Cayan, S., *et al.*, The effect of microsurgical varicocelectomy on serum follicle stimulating hormone, testosterone and free testosterone levels in infertile men with varicocele. BJU Int, 1999. 84(9):1046-9.
- 252. Paduch, D.A. and J. Niedzielski, Semen analysis in young men with varicocele: preliminary study. J Urol, 1996. 156(2 Pt 2):788-90.
- 253. Goldstein, M. and J.F. Eid, Elevation of intratesticular and scrotal skin surface temperature in men with varicocele. J Urol, 1989. 142(3):743-5.
- 254. Lee, J.D., S.Y. Jeng, and T.H. Lee, Increased expression of hypoxia-inducible factor-1alpha in the internal spermatic vein of patients with varicocele. J Urol, 2006. 175(3 Pt 1):1045-8; discussion 1048.
- 255. Ozbek, E., et al., The role of adrenomedullin in varicocele and impotence. BJU Int, 2000. 86(6):694-8.
- 256. Agarwal, A., et al., Role of oxidative stress in pathogenesis of varicocele and infertility. Urology, 2009. 73(3):461-9.
- 257. Diamond, D.A., et al., Is adolescent varicocele a progressive disease process? J Urol, 2004. 172(4 Pt 2):1746-8; discussion 1748.
- 258. Diamond, D.A., *et al.*, Relationship of varicocele grade and testicular hypotrophy to semen parameters in adolescents. J Urol, 2007. 178(4 Pt 2):1584-8.
- 259. Sayfan, J., et al., Varicocele treatment in pubertal boys prevents testicular growth arrest. J Urol, 1997. 157(4):1456-7.
- 260. Thomas, J.C. and J.S. Elder, Testicular growth arrest and adolescent varicocele: does varicocele size make a difference? J Urol, 2002. 168(4 Pt 2):1689-91; discussion 1691.
- 261. Kolon, T.F., *et al.*, Transient asynchronous testicular growth in adolescent males with a varicocele. J Urol, 2008. 180(3):1111-4; discussion 1114-5.
- 262. Kozakowski, K.A., *et al.*, Peak retrograde flow: a novel predictor of persistent, progressive and new onset asymmetry in adolescent varicocele. J Urol, 2009. 181(6):2717-22; discussion 2723.
- Alukal, J.P., et al., Testicular hypotrophy does not correlate with grade of adolescent varicocele. J Urol, 2005. 174(6):2367-70, discussion 2370.

- 264. Koyle, M.A., *et al.*, Laparoscopic Palomo varicocele ligation in children and adolescents: results of 103 cases. J Urol, 2004. 172(4 Pt 2):1749-52; discussion 1752.
- 265. Goldstein, M., Adolescent varicocele. J Urol, 1995. 153(2):484-5.
- 266. Cayan, S., et al., Adolescent varicocele repair: long-term results and comparison of surgical techniques according to optical magnification use in 100 cases at a single university hospital. J Urol, 2005. 174(5):2003-6; discussion 2006-7.
- 267. Kass, E.J. and A.B. Belman, Reversal of testicular growth failure by varicocele ligation. J Urol, 1987. 137(3):475-6.
- 268. Cayan, S., *et al.*, The effect of varicocele repair on testicular volume in children and adolescents with varicocele. J Urol, 2002. 168(2):731-4.
- 269. Lenzi, A., et al., Sperm parameters after early left varicocele treatment. Fertil Steril, 1998. 69(2):347-9.
- 270. Lemack, G.E., et al., Microsurgical repair of the adolescent varicocele. J Urol, 1998. 160(1):179-81.
- 271. Cayan, S., *et al.*, Comparison of results and complications of high ligation surgery and microsurgical high inguinal varicocelectomy in the treatment of varicocele. Urology, 2000. 55(5):750-4.
- 272. Marmar, J.L. and Y. Kim, Subinguinal microsurgical varicocelectomy: a technical critique and statistical analysis of semen and pregnancy data. J Urol, 1994. 152(4):1127-32.
- Pintus, C., et al., Varicocele in pediatric patients: comparative assessment of different therapeutic approaches. Urology, 2001. 57(1):154-7.
- 274. Esposito, C., et al., Incidence and management of hydrocele following varicocele surgery in children. J Urol, 2004. 171(3):1271-3.
- 275. Greenfield, S.P., P. Seville, and J. Wan, Experience with varicoceles in children and young adults. J Urol, 2002. 168(4 Pt 2):1684-8; discussion 1688.
- 276. Silveri, M., et al., Subinguinal microsurgical ligation--its effectiveness in pediatric and adolescent varicocele. Scand J Urol Nephrol, 2003. 37(1):53-4.
- 277. Salzhauer, E.W., A. Sokol, and K.I. Glassberg, Paternity after adolescent varicocele repair. Pediatrics, 2004. 114(6):1631-3.
- 278. Schlesinger, M.H., I.F. Wilets, and H.M. Nagler, Treatment outcome after varicocelectomy. A critical analysis. Urol Clin North Am, 1994. 21(3):517-29.

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This publication will be a benefit to pediatric urologists, caretakers, and—most of all—our patients born with genital anomalies.

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