Restoring normal anatomy in female patients with atypical genitalia

Laurence S. Baskin, MD
UCSF Benioff Children’s Hospital, 1825 Fourth St, 5th Floor, San Francisco, CA 94143

ARTICLE INFO

Keywords:
Congenital adrenal hyperplasia
Surgical treatment
Urogenital sinus
Genital development

ABSTRACT

Female patients with congenital adrenal hyperplasia (CAH) have varying degrees of atypical genitalia secondary to prenatal and postnatal androgen exposure. Surgical treatment is focused on restoring normal genitalia anatomy by bringing the vagina to the normal position on the perineum, separating the distal vagina from the urethra, forming a normal introitus and preserving sexual function of the clitoris by accepting moderate degrees of hypertrophy as normal and strategically reducing clitoral size only in the most severely virilized patients. There remains a need for continued monitoring of patients as they go through puberty with the possibility of additional surgery for vaginal stenosis. Anatomically based surgery and refinement in surgical techniques with acceptance of moderate degrees of clitoral hypertrophy as normal should improve long-term outcomes.

© 2017 Elsevier Inc. All rights reserved.

Babies born with atypical genitalia defined as discordance between external genitalia and gonadal and chromosomal sex have been classified as having a disorder of sex development (DSD) although terminology remains controversial.\(^1\) The incidence of DSD is approximately 1 in 1000–4500 live births depending on which conditions are included.\(^2\) The birth of an infant with atypical genitalia presents a unique set of challenges. Psychosexual development is influenced by multiple factors including the genes involved in sexual differentiation, gender differences in brain structure, prenatal androgen exposure, and cultural and religious influences.

The most common form of DSD presenting with atypical genitalia is 46,XX congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency comprising 90–95% of all cases.\(^3\) Rarer forms of CAH include 11β-hydroxylase CAH, 3β-HSD CAH, 17α-hydroxylase CAH and lipoid CAH. Patients with 21-hydroxylase deficiency are a relatively homogenous group of patients, most of whom present in the newborn period with atypical genitalia due to endogenous virilization and without palpable gonads. Characterizing the controversy with terminology, many patients and families reject the classification of CAH as a disorder of sex development preferring simple to use the term congenital adrenal hyperplasia as a diagnostic label once an accurate diagnosis is confirmed.\(^4,5\) Rarely, 46,XX individuals with CAH present with normal male genitalia (Prader V virilization) but without palpable gonads.\(^6\) In patients without salt-losing forms of CAH, these individuals typically present later in life after being raised as males. This is now a rare occurrence in the United States with mandatory screening of newborns allowing for early detection of classical cases of CAH.

A unique characteristic of patients with virilization of the external genitalia secondary to endogenous androgens from adrenal enzymatic defects is that they have normal female anatomy that has been virilized, i.e., a vagina, uterus, cervix and ovaries, as well as normal female fertility potential. An understanding of normal genital embryology sheds light on how this can occur. Male and female genital development

Funding source: All phases of this study were supported by an NIH Grant, R01DK058105.
E-mail address: Laurence.Baskin@ucsf.edu

http://dx.doi.org/10.1053/j.semperi.2017.03.011
0146-0005/© 2017 Elsevier Inc. All rights reserved.
diverges from the indifferent stage at approximately 8 weeks’ gestation under the influence of androgens. In the male, the urethral groove fuses in a proximal to distal fashion to form the tubular urethra. Urethral formation is complete by ~17 weeks’ gestation along with fusion of the ventral foreskin and a natural progression from early developmental curvature of the penis to a straight penis. In both the male and female, an androgen-independent canalization process occurs, opening up the urethral plate to a urethra groove in males and vestibular groove in females. What distinguishes females from males is the absence of the fusion event or formation of the tubular urethra. Interestingly, in females the normal male fusion may occur for example in patients with CAH who are exposed to androgens prenatally.

It is accepted that the amount and timing of the prenatal androgen exposure will determine the severity of the male virilization of the normal female fetus. Excessive androgen during the first trimester of fetal life impacts the amount of fusion of the bipotential genitalia externally and the location of the confluence of the urethra, vagina, and common urogenital channel internally. Excess androgen later in fetal life cannot affect genital differentiation but does affect the amount of clitoral hypertrophy. Presumably, patient’s with more severe amounts of prenatal androgen exposure will have a longer common urogenital channel and a higher confluence of the vagina and urethra connection closer to the bladder in contrast to lesser androgen exposure that will result in a lower confluence. The confluence can be visualized by radiographic imaging by injecting contrast into the common urogenital channel (genitogram).

Virilization of the external genitalia is also dependent on the amount of prenatal androgen exposure. The more extensive the androgen exposure the greater the clitoral hypertrophy or Prader stage.

Reconstructive treatment of CAH diagnosed at birth to restore normal anatomy is generally performed in the first year of life. The goal of surgery is to separate the vagina from the urethra and to restore the continuity of the vagina to a normal position on the perineum. This translates into reconstructing the common urogenital sinus single opening into a separate urethra and vaginal opening along with formation of

![Fig. 1](image-url) – Optical projection tomography imaging of human fetal genital specimens at (A) 8 weeks’ gestation (indifferent stage) where the male and female genitalia are indistinguishable. (B and C) Male and female at 9 weeks’ gestation, respectively. (D and E) Male and female at 10.5 weeks’ gestation, respectively. Note that the male specimens form a urethral groove (thin light gray arrow) from fusion of the urethral folds (horizontal gray arrow in D). Both the male and female specimens undergo canalization of the urethral plate (short dark gray arrows B and D). The female specimens do not undergo fusion resulting in a vestibular groove (thin light gray arrow C and E).

![Fig. 2](image-url) – Schematic representation of anatomy of females with virilization secondary to congenital adrenal hyperplasia. (A) High confluence. Note that the urethra and vagina meet close to the bladder neck. (B) Low confluence. Note that the urethra and vagina meet closer to the opening of the common urogenital sinus on the underside of the hypertrophied clitoris.
an introitus with the mucosal tissue and formation of a labia minora and majora.9–11

The technique of restoring normal female anatomy has evolved over time based on a better understanding of normal female neuroanatomy.9–18 The key breakthrough relates to treating the vagina and urethra/bladder as a unit to facilitate separation of the confluence of the urethral and vagina (Fig. 2).17,19,20 The common urogenital channel can be repositioned as the urethra under the clitoris with excess common urogenital sinus used to reconstruct the anterior vagina wall and mucosa-lined introitus.11 If the vagina does not reach out to the perineum, a posterior skin flap (Fortunoff) can facilitate reconstruction of the posterior vagina wall.17,19,20 The “virilized” labia can be reduced in size from the effects of the prenatal androgen exposure to resemble labia majora and minora and a clitoral hood fashioned to cover the typically enlarged clitoris. As noted, emphasis is on the preservation of sexual function in contrast to reducing the clitoris to a normal size.15,22–24 In adult life, patients can always request further reconstructive surgery which, based on personal observation, does not appear to be a common occurrence. Initial concerns about long-term urinary continence after urogenital sinus mobilization after potty training have not been reported although long-term follow-up studies are warranted for clinical confirmation.25–27

The description of total urogenital mobilization by Peña20 signaled a significant advance in the surgical management of CAH. The basic technique involves a 360° mobilization of the entire urogenital sinus, which is then brought to the

Fig. 3 – Genitogram of a patient with congenital adrenal hyperplasia (contrast injected into the common urogenital sinus retrograde) showing the high confluence, the vagina, cervix, uterus, bladder, and urethra.

Fig. 4 – Examples of progressively more severe cases of virilization secondary to congenital adrenal hyperplasia. (A) Prader I, (B) Prader II, (C) Prader III, (D) Prader IV, and (E) Prader V (white arrows represent single common urogenital sinus opening). Note the progressively more severe clitoral hypertrophy.
perineum. In partial urogenital mobilization, dissection is avoided superior to the urethra under the pubic bone, a nerve-rich zone that contains the sphincteric musculature necessary for urinary continence. Long-term follow-up is now being reported confirming normal continence.

The hypertrophied clitoris, except in the most severe cases (i.e., when the appearance is that of a penis) can be often be left with moderate amounts of hypertrophy and covered with a reconstructed clitoral hood. In severe cases of clitoral hypertrophy, nerve-sparing reduction on the ventral aspect can be performed with an understanding of the neuroanatomy and hence preservation of future sexual function and reducing clitoral size. These surgical recommendations are consistent with the consensus statement on 21-hydroxylase deficiency from the Pediatric Endocrine Society and the European Society for Pediatric Endocrinology.

Systematic long-term evaluation is lacking for reconstruction for patients with CAH. Nevertheless, women with CAH who have had surgical restoration of normal female anatomy in childhood are generally in agreement that they are pleased that they had surgical reconstruction early in life as opposed to later in life when they could personally assent or consent to the operation. A cohort of women with CAH surgically treated later in life (or treated without surgical reconstruction) does not presently exist as a comparison group.

Thus based on expert opinion, the overwhelming majority of surgical specialists continue to recommend restoration of normal anatomy in female patients in early childhood. Factors that influence this decision include the smaller distance between the perineum and normal vagina in childhood as opposed to after puberty, the better healing prospects in young children and the possible facilitating effects of maternal estrogen on reconstruction in young infants.

Special considerations with surgery include the need for long-term follow-up and the likelihood that patients will need additional procedures at the time of sexual maturity specifically to ensure that the vagina is of adequate caliber for satisfactory sexual intercourse. This may simply involve an exam under anesthesia and/or revision of the distal vagina for inadequate caliber (vaginal stenosis). At this time in life, the surgery is typically elective facilitating post-operative participation of the patient if temporary vaginal dilation is necessary after correction of vaginal stenosis. Retrospective studies have documented a decrease in clitoral sensitivity after clitoral surgery. The majority of long-term studies, however, have not shown a significant change in sexual function or satisfaction in patients undergoing corrective surgery for virilization secondary to congenital adrenal hyperplasia. Patients that have had clitoral surgery where the clitoris is recessed by suturing the clitoral erectile tissue to the pubic bone have reported pain on sexual arousal. This type of clitoroplasty is no longer recommended and surgical release to alleviate pain has been required in some patients. Additionally, as is recommended for hypospadias reconstruction all patients should be assessed for satisfactory cosmetic and functional outcomes after puberty. This would include validated sexual and societal function questionnaires, assessment of surgical outcomes by patient and investigator in respect to sensation and anatomical function including vagina and clitoral outcomes and associated issues such as urinary tract infections and/or urinary continence, fertility, and childbirth.

REFERENCES