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Restoring normal anatomy in female patients with atypical genitalia

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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.

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 case.[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 patents 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

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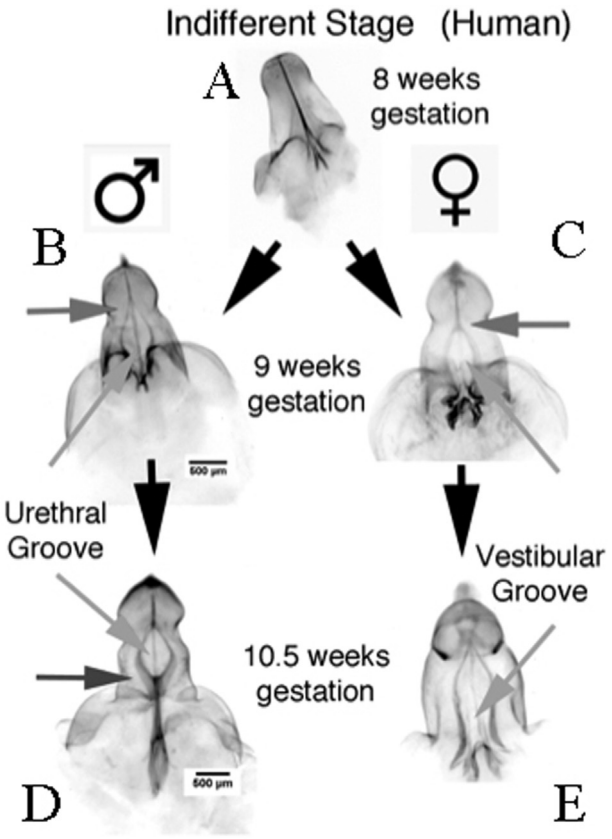

Fig. 1 – Optical projection tomography imaging of human fetal genital specimens at (A) 8 weeks' gestation (indifferent stage) where the male and female genitalia are indistinguishable. (B and C) Male and female at 9 weeks' gestation, respectively. (D and E) Male and female at 10.5 weeks' gestation, respectively. Note that the male specimens form a urethral groove (thin light gray arrow B and D) 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).

diverges from the indifferent stage at approximately 8 weeks' gestation under the influence of androgens (Fig. 1).[7] 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 the 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 (Fig. 1C and E).[8] 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 (Fig. 2). The confluence can be visualized by radiographic imaging by injecting contrast into the common urogenital channel (genitogram) (Fig. 3).

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 (Fig. 4).

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

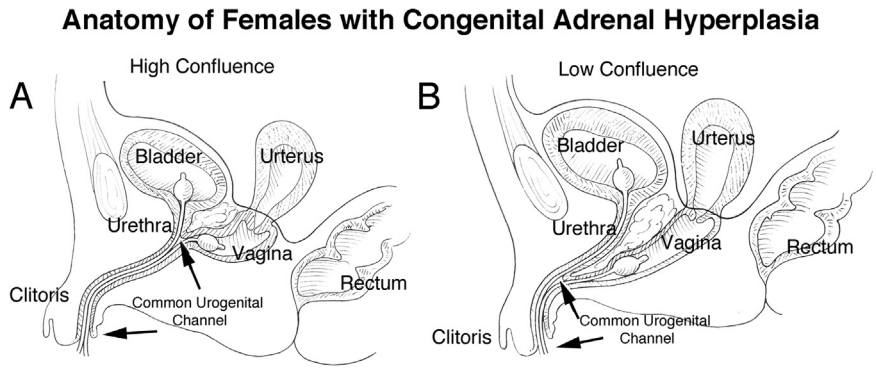

Fig. 2 – Schematic representation of anatomy of females with virilization secondary to congenital adrenal hyperplasia. (A) High confluence. Note that the urethra and vagina meet close to the bladder neck. (B) Low confluence. Note that the urethra and vagina meet closer to the opening of the common urogenital sinus on the underside of the hypertrophied clitoris.