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5 α -reductase-2 Deficiency's Effect on Human Fertility

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Abstract

A most interesting and intriguing male disorder of sexual differentiation is due to 5 α -reductase-2 isoenzyme deficiency. These males are born with ambiguous external genitalia due to a deficiency in their ability to catalyze the conversion of testosterone to dihydrotestosterone (DHT). DHT is a potent androgen responsible for differentiation of the urogenital sinus and genital tubercle into the external genitalia, urethra and prostate. Affected males are born with a clitoral-like phallus, bifid scrotum, hypospadias, blind shallow vaginal pouch from incomplete closure of the urogenital sinus and a rudimentary prostate. At puberty, the surge in mainly testosterone production prompts virilization, causing most to choose gender reassignment to male.

Fertility is a challenge for affected men for several reasons. Uncorrected cryptorchidism is associated with low sperm production, and there is evidence of defective transformation of spermatogonia into spermatocytes. The underdeveloped prostate and consequent low semen volumes affect sperm transport. Additionally, semen may not liquefy due to a lack of prostate-specific antigen. In this review, we discuss the 5 α -reductase-2 deficiency syndrome and its impact on human fertility.

INTRODUCTION

Male reproductive development

The development of normal male reproductive function involves several key steps. A euploid 46XY conceptus directs the bipotential gonad to develop into testes during the fifth week of gestation. This is accomplished at the intracellular level by SRY gene activation of SOX-9, which up-regulates and creates a feed-forward loop with FGF-9, and which in turn promotes the formation and proliferation of Sertoli cells. Primordial germ cells then migrate into this developing gonad and begin to form prospermatogonia.

At puberty, spermatogenesis is initiated by rising gonadotropin levels. Natural reproduction requires transport of spermatozoa produced in the testes through the ejaculatory duct via

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Wolffian duct derivatives: the epididymides, vasa deferentia, and seminal vesicles. Once sperm reach the seminal vesicles, effective transport requires developed external genitalia and a functioning prostate. The prostate produces seminal fluid as well as prostate-specific antigen that prevent coagulation of seminal fluid. Whereas proper internal duct development is dependent on testosterone as the intracellular mediator, development of the urogenital sinus and tubercle into the external genitalia, urethra and prostate requires conversion of testosterone to dihydrotestosterone (DHT) by the isoenzyme 5 α -reductase-2.

5 α -reductase-2 enzyme

There are two 5 α -reductase isoenzymes. The 5 α -reductase-1 gene maps to the short arm of chromosome 5 band 15. In adulthood, it is expressed mainly in the liver and non-genital skin and is expressed in very low levels in the prostate, genital skin, and internal duct structures (1). The physiological function of type-1 isoenzyme in humans remains obscure, although there is limited evidence of a role in murine parturition (2). The 5 α -reductase-2 gene is located on the short arm of chromosome 2 band 23. This gene's enzyme product is expressed in high levels in the epididymides, seminal vesicles, prostate, genital skin and liver. It is the gene mutated in subjects with 5 α -reductase-2 deficiency (3).

To date, over 60 mutations of the 5 α -reductase-2 gene have been identified (4), including the mutations affecting the three largest kindreds: New Guinean, Dominican and Turkish (5–11) the condition is inherited as autosomal recessive (Figure 1). The New Guinean kindred's particular mutation was the first group described. This kindred's affected males have a deletion of the 5 α -reductase 2 gene of more than 20 kb resulting in a loss of enzymatic activity (8). The Dominican kindred have a missense mutation in exon 5, substituting thymidine for cytosine and resulting in a substitution of tryptophan for arginine at position 246. There is a consequent reduction in binding of 5 α -reductase-2 to its critical cofactor NADPH and a dramatic decrease in enzymatic activity (9). Finally, the Turkish kindred have a single base deletion in exon 5, causing a frame shift mutation with complete loss of enzymatic activity (10, 11). These kindreds' mutations arose due to their geographic isolation and resultant inbreeding, allowing a rare enzymatic defect inherited in an autosomal recessive manner to prevail in small ethnic groups.

Although three representative mutations identified in the three largest pedigrees of 5 α -reductase-2 deficiency are described above, there are documented mutations in all five exons of the gene, ranging from a single point defect to a deletion of the entire gene as noted in Figure 1(1, 4, 5). The varieties of consequent enzymatic dysfunction resulting from these mutations include impaired binding of substrate and cofactor to the isozyme, blocked formation of a functional isozyme (deletion, nonsense mutation, or splice-junction alterations), and an unstable isozyme resulting in DHT deficiency due to a decreased conversion of testosterone to DHT (5).

DHT and the androgen receptor

Both testosterone and DHT are competitive agonists at the same androgen receptor. The androgen receptor is a ligand-dependent nuclear transcription factor that binds with higher affinity to DHT, allowing for potent androgen effects. Upon attachment of androgen to the

hormone-binding domain of the androgen receptor, conformational changes allow the complex to enter the nucleus, where it activates target-gene transcription through a DNA-binding domain interacting with the androgen-response element, producing protein products that effect androgen action. The DNA-binding domain of the androgen receptor shares sequence areas with progesterone, mineralocorticoids, and glucocorticoids, but is most analogous to the progesterone receptor. Progesterone is also a substrate of the 5 α -reductase-2 isoenzyme, which converts it to dihydroprogesterone, a hormone that in turn competes with testosterone and DHT for the androgen receptor (12).

CLINICAL PRESENTATION

The phenotypic presentation of males affected with 5 α -reductase-2 deficiency is well-characterized (6, 13). The affected subjects are 46XY males with testes and male accessory ducts but predominantly female external genitalia. Because the Wolffian ducts develop normally owing to normal fetal testosterone levels, the ejaculatory ducts, epididymides, vasa deferentia, and seminal vesicles are formed. However, since external genitalia development is dependent on intracellular conversion of testosterone to DHT, the urogenital sinus and genital tubercle fail to differentiate normally into the external genitalia, urethra and prostate. At birth, males homozygous for 5 α -reductase-2 mutation typically have a clitoral-like phallus, bifid scrotum, hypospadias, blind shallow vaginal pouch from incomplete closure of the urogenital sinus and a rudimentary prostate (Figure 2 and Figure 3). Because of this genital ambiguity, most males are assigned a female gender at birth and reared as such. At puberty, the surge in mainly testosterone production causes individuals to virilize, with a noticeable increase in muscle mass, deepening of the voice, and an increase in libido, prompting most to transition to the male gender. This pubertal rise in androgens increases penile length, results in scrotal rugation and pigmentation, and is involved in testicular descent. These testosterone-driven pubertal developments underscore the difference between testosterone versus DHT-mediated action (Table 1). After puberty, there is also a noticeable sparsity of body hair and lack of hairline recession—both of which are mediated by DHT which is decreased in males with this condition. In most cases, final adult height is commensurate with unaffected siblings. Post-pubertal studies of subjects with this condition led to the development of 5 α -reductase-2 inhibitors for the treatment of BPH and male pattern baldness (6,13,46,49,50). Gynecomastia—as observed in androgen-insensitivity syndrome—is absent in 5 α -reductase-2-deficient males. Females homozygous for the 5 α -reductase-2 mutation have been observed to have normal development of internal and external genitalia. They have reduced body hair, delayed menarche and are fertile with unremarkable gonadotropin levels; two of the three homozygous females gave birth to twins (14).

Hormonal diagnosis

The phenotypic appearance of affected males at birth often parallels androgen-deficient states. Because androgen-insensitivity syndrome and defects of testosterone synthesis may have similar presentations to 5 α -reductase-2-deficient newborns, measurement of the T/DHT ratio is a first-line diagnostic test. However, in infants and pre-pubertal children, basal androgen levels are insufficient to make a clear diagnosis. Exogenous hCG

administration is required to obtain sufficient testosterone and DHT levels to demonstrate elevated T/DHT ratios in this condition (15). A T/DHT ratio greater than 8.5 is suggestive of the deficiency and these neonates should be investigated further with molecular analysis of the 5 α -reductase-2 gene. (16, 17) Adult subjects deficient in 5 α -reductase-2 activity also have elevated T/DHT ratios with normal-to-elevated testosterone levels compared with normal subjects with defects in testosterone synthesis. 5 α -reductase-2 subjects both adults and children also have abnormal ratios of 5 β - to 5 α -reduced glucocorticoid and other steroid metabolites, indicating that this condition is a generalized defect in hepatic steroid 5 α -metabolism, clearly distinguishing them from androgen-insensitive subjects who may also have abnormal T/DHT ratios (18).

Gender Identity and Gender Role

If the condition is not diagnosed in infancy or childhood, subjects with 5 α -reductase-2 deficiency have been reported to frequently undergo a change in gender role during or after adolescence, confirming our first reports (6, 13, 18–20). In the Dominican community, at puberty a change in gender from female to male occurred in the vast majority of subjects who were unambiguously reared as females (6, 13, 18–20). Data available for 18 subjects revealed that 16 successfully changed to a male gender role. These subjects became convinced of their male gender identity during adolescence. Gender role change occurred on average at 16 years of age, with a range of 14–24 years. Fear of harassment by local villagers caused some hesitation in changing until they were confident of their ability to defend themselves (6, 13, 19–20). Their male behavioral pattern in adulthood has been observed for over twenty years.

The social and psychosexual development of New Guinean male pseudohermaphrodites of the Sambian tribe with 5 α -reductase-2 deficiency has been recorded over three decades (21–24). The Sambian tribal culture of the eastern highlands is rigidly gender-segregated and includes traditional pubertal male initiation rites (23). In the past, some New Guinean 5 α -reductase deficient subjects were raised as girls until puberty, whereupon they made a difficult transition to male (23). Today, however, the deficiency is usually recognized in childhood, as it is by experienced midwives in the Dominican cohort. The term “turnim-man,” derived from the Melanesian pidgin, connotes gender role transformation and the belief that these anatomically ambiguous individuals are innately, and biologically, driven to masculinize (25). In addition to these well-studied kindreds, gender change has been noted in affected subjects from many countries (26–34). If puberty occurs without surgical and hormonal or societal reinforcement of the assigned female sex, then a male gender identity, although discordant with the sex of rearing, will prevail; it appears that androgen (i.e., testosterone) exposure of the brain in utero and during the early postnatal period and puberty often overrides the sex of rearing as well as sociocultural influences in determining male gender identity. While the majority of genotypic males born with 5 α -reductase-2 deficiency and ambiguous genitalia are assigned female gender at birth, approximately 63% of studied individuals choose to live as males at puberty (35). Though maintenance of a female gender identity in adulthood has been reported, long-term psychosexual follow-up, critical to determination of gender identity, is not available for most subjects. For societal reasons, subjects may choose to conceal their gender identity and live as females, their genotypic

gender identity never to be revealed. For example, we studied a 65-year-old male pseudohermaphrodite with a 5 α -reductase deficiency who was born in Italy and raised as a girl before immigrating to the United States at age 16. Lengthy psychosexual evaluation revealed that although he self-identified as male, a female role was maintained due to family pressures (19).

Theoretically, masculinization of the brain occurs under the influence of testosterone, during the prenatal and/or neonatal period and together with the activation of a testosterone-mediated puberty, a male gender identity develops, overriding the female sex of rearing. This experiment of nature emphasizes the importance of androgens, which act as inducers and activators in evolution of male gender identity in man (5, 6, 13, 18–20). In subjects with inadequate testosterone production or action, if adequate androgen imprinting has not occurred, the sex of rearing may become the predominant factor.

TREATMENT

Hormonal and surgical treatment can improve external appearance and optimize sexual function. In infancy or in childhood, DHT gel (5–10mg/day) can be administered to increase penile length with maximal length achieved at six months of treatment (36). Since affected males have normal testosterone production, testosterone supplementation is not necessary. Surgical correction consists of resection of the vaginal pouch, urethroplasty for hypospadias, and orchiopexy to resolve cryptorchidism. Multiple surgical procedures are often necessary to achieve optimal phenotypic outcomes.

MANAGEMENT

Every effort should be made to accurately diagnose a newborn with ambiguous genitalia. With a thorough understanding of anticipated events at puberty, an initial male sex assignment should be considered. Long-term follow up has shown that many affected individuals who live as male are participating in long-term, heterosexual relationships (37). If fertility is desired, most of these couples will require assisted methods of reproduction (38). If azoospermia is observed in the ejaculate, these males are candidates for testicular micro-dissection with harvest of seminiferous tubules.

SPERMATOGENESIS AND BARRIERS TO FERTILITY

Spermatogenesis is initiated by genes located on the long arm of the Y chromosome and completed under the influence of pituitary gonadotropins. Diploid spermatogonia increase in size to become primary spermatocytes. The first meiotic division of primary spermatocytes produces two haploid secondary spermatocytes, which then undergo a second meiotic division to give rise to four spermatids. The resulting spermatids mature into spermatozoa within the testis. Approximately 70 days elapse for a primary spermatocyte to reach the spermatozoan stage, and another 12–21 days for transport of sperm from the testis through the epididymis and into the ejaculatory duct. Sperm maturation is facilitated by the action of pituitary gonadotropins, stimulating Sertoli cell production of androgen-binding protein and various cofactors. The primary role of the Sertoli cell is to promote and maintain germ cell development via maintenance of the unique microenvironment within the lumen of the

seminiferous tubules. Fertility is a challenge for males homozygous for the 5 α -reductase-2 gene mutation. Since affected males have a normal male genotype, primary testicular development is expected. However, because testicular migration through the inguinal canal is often arrested, the intrainguinal temperature may adversely impact spermatogenesis. Although oligospermia may be a consequence of cryptorchidism, spermatogenesis itself may be impaired from deficient 5 α -reductase-2 activity (39). Consequently, the question of whether spermatogenic impairment in 5 α -reductase-2 deficient males is a direct result of the gene mutation or a secondary consequence of incomplete testicular descent remains open. Testicular histopathology of males homozygous for the 5 α -reductase-2 mutation has been studied alongside males with isolated cryptorchidism in an attempt to address this question (40).

In 5 α -reductase-deficient males, there was a normal germ cell population but a lack of primary spermatocytes found on biopsy. Males with isolated cryptorchidism appeared to have a decreased number of germ cells and evidence of primary spermatocytes. This suggests that DHT plays a role in growth and differentiation of spermatocytes. It has also been suggested that subfertility in males with 5 α -reductase-2 deficiency may be a consequence of an intrinsic failure of the Sertoli cell to reach a fully functional state at puberty (41, 42). As the phenotypes of this disease range widely, so do the testicular histology of affected males, from normal to complete absence of germ cells.

Since males homozygous for the 5 α -reductase-2 mutation have normal or even high testosterone serum levels associated with relatively low DHT levels, in the peripheral circulation, they can serve as paradigms for studying the relative roles of testosterone and DHT in spermatogenesis. In males with normal enzymatic activity, intratesticular testosterone concentrations are approximately 600ng/mL—well in excess of the average serum testosterone concentration (5ng/mL). In contrast, intratesticular DHT levels are only 2% that of testosterone, implying that testosterone, rather than DHT, plays the major role in spermatogenesis (43). Although there are no specific studies measuring the intratesticular testosterone and DHT levels in males who are homozygous for the 5 α -reductase-2 mutation, semen analyses of such patients with bilaterally descended testes suggest that DHT appears to be more important in regulating semen volume and viscosity rather than playing a major role in spermatogenesis (especially if normal testosterone concentrations are present) (39). In addition, when hypogonadal mice receive supplemental testosterone and DHT, spermatogenesis has been restored (44). The normal-to-elevated testosterone levels of males homozygous for 5 α -reductase-2 gene mutation in combination with the diminished levels of DHT in the testes suggest that spermatogenesis can occur in the presence of decreased DHT. On the other hand, clinical trials for benign prostatic hypertrophy indicate that when DHT levels are lowered by finasteride, a 5 α -reductase-2 inhibitor, normal men exhibit a drop in total sperm counts, sperm concentration and sperm volume, which appear reversible after discontinuation of the drug (45).

It is known that secretions by the prostate, seminal vesicles, and distal vasa deferentia are responsible for the total semen volume. Males affected with 5 α -reductase-2 deficiency have non-palpable prostates on rectal exam, prostates that are 1/10 the volume of normal males on MRI (1, 6, 46). Thus, in these individuals, sperm transport is affected by the low semen

volumes as well as the failure of semen to liquefy from deficient prostate-specific antigen—a serine protease (39). Their ejaculates are typically of low volume, gel-like, and fail to liquefy with resultant impeded sperm motility and transport through the female genital tract. Finally, a shortened phallus and perineal hypospadias, if not surgically corrected, present obvious physical barriers to intromission and natural conception.

PATERNITY

Reports of paternity through natural conception and intrauterine insemination reveal the degree of variability in spermatogenesis of affected males (47). Males found to have normal or near normal sperm concentrations and reasonable motility should first attempt intrauterine insemination (IUI). Most often, the semen analysis of affected males reveals severe oligoasthenoteratospermia, low semen volume, and failure of the semen to liquefy, precluding paternity through insemination. IVF/ICSI is the appropriate treatment for these patients (48). The first reported case of paternity through IUI involved a 36-year-old Dominican male homozygous for a thymidine-to-cytosine substitution in exon 5 of the 5 α -reductase-2 gene. At birth he was noted to have ambiguous genitalia and bilaterally descended testicles. During puberty, he underwent deepening of the voice and penile enlargement to a stretched length of 3.5cm. Testicular volume, 25mL on the right and 20mL on the left, was normal and the prostate gland was not palpable. At age 34 he was treated with 25mg of topical DHT cream for 7 months, achieving a final penile length of 7.5cm. His wife was an unrelated healthy female with normal menstrual cycles and sequencing of her 5 α -reductase-2 gene revealed no abnormalities. Semen analysis revealed low semen volumes but normal concentrations and motility. All specimens were noted to be extremely viscous with initial semen volumes ranging from 0.2–0.5mL, with concentrations ranging from 65 to 350 $\times 10^6$ mL, and motility ranges of 33–61%. Each semen sample was prepared in the standard fashion using a Percoll gradient and final pellet resuspension in 0.5mL of fresh medium.

After appropriate genetic counseling, the subject's wife was monitored in a natural cycle and an intrauterine insemination was performed 25 hours following the LH surge. Conception occurred on the third attempt to achieve the first pregnancy and on the second attempt to achieve the second pregnancy. The initial pregnancy resulted in premature rupture of the membranes at 33 weeks followed by a cesarean section resulting in a healthy male with normal external genitalia. The second pregnancy resulted in healthy male and female dizygotic twins delivered via repeat cesarean section.

Paternity through IVF has also been reported in a 33-year-old Dominican male with the identical thymidine-to-cytosine substitution known to be common in the Dominican kindred. This patient's testes did not descend until puberty. His stretched penile length was 5cm. He was noted to have testicular volumes of 14mL and 16mL of right testicle and left testicle, respectively. Initial sperm counts were unquantifiable owing to the high degree of semen viscosity and failure to liquefy. Semen volumes were 0.1mL, sperm density of 8.4 $\times 10^6$ mL, and motility of less than 1%. His wife was an unrelated normally menstruating female without 5 α -reductase-2 gene abnormalities. Following appropriate genetic counseling, she underwent luteal suppression and stimulation with 200 IU/d of recombinant FSH. Ovulation

was triggered on the twelfth day with 5,000 IU hCG when two lead 17mm follicles were present. Four of nine mature oocytes were fertilized with intracytoplasmic sperm injection. Two eight-cell embryos were transferred on day 3, resulting in a twin gestation. Premature rupture of the membranes occurred at 36 weeks of gestation and a healthy male and female were delivered via cesarean section. These examples highlight both the variability in semen parameters in men with 5 α -reductase-2 gene mutation as well as the need for individualization in choosing the appropriate treatment regimens.

CONCLUSION

Our current understanding of male sexual differentiation has been facilitated by the study of males homozygous for the 5 α -reductase-2 gene mutation (1, 3). Conversion of testosterone to DHT by 5 α -reductase-2 is necessary for differentiation of the external genitalia, urethra, and prostate and for testicular descent. Thus, these affected individuals present with clitoral enlargement, bifid scrotum, hypospadias and blind vaginal pouch and rudimentary prostate. Virilization at puberty is a hallmark of this disease, prompting many reared as female to choose a male gender role. For those who choose a male gender role and desire children, fertility is possible. Because most affected males have low sperm production, either from uncorrected cryptorchidism or an arrest in development in spermatogenesis, assisted fertilization with IVF is often necessary. Urologic interventions to optimize male external genitalia should be considered before assisted reproductive technology is used. It is also critical for couples to consult with a reproductive medicine center with adequate experience in sperm preparation techniques for samples deficient in prostatic enzymes and with the use of intracytoplasmic sperm injection in severe cases. Judicious use of gonadotropins in female partners will minimize the risk of ovarian hyperstimulation syndrome and optimize oocyte quality. Finally, management of couples with affected male partners should also include psychosocial and genetic support. Using this multidisciplinary approach, males homozygous for the 5 α -reductase-2 mutation can achieve biological paternity.

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Figure 1.

An illustration of gene mutations in the human 5 α -reductase-2 gene. The 61 mutations identified in the 5 α RD2 gene, so far, are found throughout all five exons of the gene, and range from a single-point defect to a gene deletion.

These mutations include 50 missense mutations, six small deletions, three splicing junction alterations, one single nucleotide insertion, and a large deletion involving the entire gene. Adapted and updated from reference 5 (Zhu YS and Imperato-McGinley J: *Disorders in male sexual differentiation: molecular genetics, gender identity, and cognition, in Hormones, Brain and Behavior*. Pfaff DW, Arnold AP, Etgen AM, Fahrbach SE and Rubin RT (eds), 2nd ed, Vol 5, Academic Press, San Diego, CA. pp2787–2824, 2009).

Figure 2.

Illustration of the role of testosterone and dihydrotestosterone in male sexual differentiation *in utero*. Adapted from reference 6 (Imperato-McGinley J, Guerrero L, Gautier T, and Peterson RE (1974) Steroid 5 α -reductase deficiency in man: An inherited form of male pseudohermaphroditism. *Science* 186:1213–1216).

Table 1

Androgen Action at Puberty. Adapted from Zhu YS and Imperato-McGinley J: *Male pseudohermaphroditism due to 5 α -reductase-2 deficiency*. In: *Gynecology and Obstetrics*, Sciarra JJ (ed), Lippincott Williams & Wilkins, Chicago, IL, Volume 5, Chapter 81, 2004, CD version.

Testosterone	Dihydrotestosterone
Anabolic Actions	Increased facial, body hair
Muscle mass increased	Scalp hair recession
Penis enlargement	
Scrotum enlargement	Prostate enlargement
Vocal cord enlargement	
Skeletal maturation	Acne
Growth spurt	
Epiphyseal closure	Pituitary-gonadal feedback
Spermatogenesis	
Male sex drive, performance	
Pituitary-gonadal feedback	