

Fully Masculinized 46,XX Individuals with Congenital Adrenal Hyperplasia: Perspective Regarding Sex of Rearing and Surgery

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Abstract

Current guidelines for gender assignment for all 46,XX congenital adrenal hyperplasia (CAH) continue to be female. This decision is most challenging for individuals with a 46,XX karyotype born with (CAH) having severely masculinized genitalia (Prader 4 or 5). They may be at significant risk for quality of life (QoL) and psychological health. More outcome information currently exists for such individuals assigned male than female. Most available data for those raised females do not indicate the extent of masculinization at birth, so there are minimal outcome data to compare with those raised males. Gender dissatisfaction among those raised females may be related to the degree of prenatal androgen excess in the brain evidenced by external genital masculinization. Also, additional brain maturation after birth, especially during puberty, is impacted by postnatal androgen excess resulting from inadequate androgen suppression. The purpose of this perspective is to suggest that both female and male assignment be considered. Most who have been raised male at birth have positive adult outcomes. This consideration should occur after discussions with full disclosure to the parents. The lack of more outcome data highlights the need for further information. This perspective also suggests that surgery should be deferred whether assigned female or male at least until gender identity is apparent to preserve the potential for male sexual function and prevent irrevocable loss of sensitive erotic tissue. While the gender fluidity is recognized, it is important to consider potential subsequent need for gender reassignment and extent of masculinization, particularly at the time of gender determination.

Keywords: Congenital Adrenal Hyperplasia, Differences of Sex Development, Disorders of Sex Development, Gender, Intersex

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According to the Endocrine Society Clinical Practice Guidelines, all genetically female individuals with congenital adrenal hyperplasia (CAH) should be assigned and raised female, even those with fully masculinized external genital maturation (1). This perspective is written to stimulate further assessment of this issue based upon outcome data and to plea for publication of more detailed outcome data. Data suggest that levels of fetal androgen play an important role in the brain sexual differentiation and has an enduring influence upon behavior (2). In situations such as CAH involving atypical androgen concentrations among genetic females during fetal life, increased male-typical juvenile behavior is well known. Alterations in gender identity and sexual orientation also occur in this situation. In addition, there is indirect evidence that elevated androgen levels occur after birth, both among genetic females with CAH and among some with polycystic ovarian syndrome (PCOS) (3). This provides

the basis for a perspective regarding the current care of newborns. We realize that our perspective may change if a treatment of CAH becomes available that results in suppression of androgen excess continually throughout childhood and adolescence. The Penn State Hershey Medical Center Institutional Review Board, Hershey, Pennsylvania, United States of America indicated that because new data regarding patients are not reported that this perspective is exempt from full committee review and approved this submission.

Currently, most demographic data about this group of patients do not include the extent of masculinization such as Prader Staging (4). However, these outcomes appear to be related to the severity of the CAH. In contrast, among those raised male because of extensive masculinization, there is considerable positive outcome information regarding employment, intimate and general social

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relationships and sexual satisfaction, although these men are infertile. The most recent summary of these outcomes was reported in 2020 (5).

This small portion of those with 46,XX and CAH who have male genitalia comprise an important focus for the current controversial viewpoints regarding the care of intersex, referred to as disorders (or differences) of sex development (DSD). This involves neonatal assignment of sex of rearing and genital surgery during infancy and childhood. Herein, we aim to present a perspective regarding the difficult choices that must be made for CAH patients with a 46,XX karyotype and male external genitalia.

The focus of this discussion is based largely upon the available adult outcome of individuals whose clinical diagnosis of CAH was missed at birth and delayed until after sex was assigned. This refers to the clinical diagnosis based on physical findings and laboratory values, while genetic mutations were not verified among all. Because of the variability of severity in CAH, a rigid diagnostic algorithm should not apply. It is our viewpoint, particularly for this masculinized group with 21-hydroxylase CAH. We agree that unique aspects of each of these individuals should be considered as discussed in publications (6, 7).

It has been presumed since the first use of glucocorticoids, about 70 years ago, that good adrenal suppression in the CAH affected patients would result in a well-adjusted adult life including fertility potential. Yet, this still has not been verified for those born with nearly or completely masculinized genitalia. Further, to date, no fully adequate therapy has been developed to suppress adrenal androgen excess throughout the 24-hour day without glucocorticoid excess.

The International Consensus Conference on Management of Intersex Disorders (Oct 28-30 2005) concluded that there were insufficient data to present the consideration of male assignment so the long-standing recommendation of a female sex of rearing was simply repeated. The most recent Endocrine Society Clinical Practice Guideline regarding CAH states that this issue is controversial while recognizing the need for full disclosure (1). In spite of the lack of fertility data among those born with essentially male genitalia raised female, the guideline further states that among the minority who were born with considerable masculinization who try to conceive may experience “near normal” pregnancies.

In the last 15 years, there has been considerable additional data illustrating positive adult outcome among those raised males such as satisfactory sexual relationships (5). This study of 128 affected that included 46 of whom were adults age 18 or over. Also, there were 11 who died in infancy, 35 who were reassigned female and 36 still minors. These 46 adult individuals were all assigned male based on Prader 4 or 5 staging (4) before the diagnosis of CAH was made. Among these adults raised male, many were in long-term relationships with females,

only 2 were reported to have gender identity problems. The other 44, although infertile, reported male gender identity and a good adult outcome based on intimate, including sexuality, relationships, general socialization and employment. Most reported being regularly sexually active with sufficient sexual arousal and potency.

Almasri et al. (8) designed a systematic analysis on the more than 1200 raised female reported female identity over the 35 years prior to Nov. 2017. These 46,XX patients with CAH deficiency were not categorized according to Prader staging (4). Among this group, 11.3% had a male gender identity (11.3%) and 23.8% homosexual. Although without verification, it can be assumed that those born with the greatest masculinization are more likely to develop problems with gender identity. Therefore, it is not far from mind that a disproportionate portion with gender identity was found in the study analysis. Although, identification a consistent gender with related rearing, sex is the golden goal in DSD management.

It is well-documented based on a review of 30 publications that patients with CAH raised female are more likely to have a sexual orientation than normal females (9). Since a homosexual outcome should not be considered a negative outcome, sexual orientation is currently not seen to be a factor for consideration.

The current standard of care must involve full disclosure to patients and for minors their parents. Therefore, parents of genetically female CAH individuals born with markedly masculinized genitalia (Prader 4 or 5) should be provided with current outcome information for those raised both female and male. The goal of the assignment of a sex of rearing is that it be consistent with gender identity that is subsequently expressed. Because of the indirect evidence that androgen excess impacts the central nervous system (CNS) development prenatally, there may be a greater tendency among those with evidence of greater exposure because of male genital external development toward a male gender identity.

This situation involves the question of whether genital surgery can occur before gender identity is manifest based on parents' decisions. It is clear from the outcome among those raised and identifying male that the male external genitalia provide for sexual function as a male. Penetrative intercourse has been reported to be satisfying and fulfilling. When raised as a male, there is no need for external genital surgery during infancy. It is appropriate to consider insertion of prosthetic testes and oophorectomy after male gender is clearly manifest, at or after the age of puberty. Conversely, the difficult surgical challenge to construct female genitalia when the sex of rearing is female suggests that surgery should be deferred in this situation until the female sex of rearing is clear.

No comparison of outcome between those raised male and female for only those with Prader 4 or 5 (4) outcome data is currently available. A recent publication (10) cites a 2005 review (11) that addressed the issue of sex of

rearing among 46,XX individuals with CAH. However, in this 2005 publication, 23 publications reported that 250 and 33 46,XX individuals were raised female and male respectively. The 250 raised female included those with Prader stages 1 to 5, without information regarding Prader 4 and 5. Among those raised male, 19 of the 33 raised male had Prader stage 4 or 5 masculinization. This portion among those raised male is disproportionate since this occurs in less than 5 percent of cases. Hence, a comparison of the 13 among the 250 raised female (5.2%) and 4 of 33 (12.1%) raised males reported to have gender dysphoria is an inappropriate comparison of different populations. Based on this previous conclusion, the 2019 summary used these data as a basis for again making the conclusion that raising all 46,XX patients as females was appropriate for all, including those markedly virilized. However, in retrospect, it appears that the groups were not comparable since those raised males almost certainly had a greater portion with Prader 4 or 5 and those cases were published because of their unique circumstance rather than as a series to evaluation gender dysphoria. Therefore, this conclusion based on non-representative data is likely inaccurate.

The basis of our opinion is the perception that the excessive androgen has a significant impact upon gender development, making it more likely that those with Prader 4 or 5 raised female will have gender identity problems. Ideally, to make an informed decision about whether male assignment is an appropriate consideration for those currently born with CAH and essentially masculinized genitalia requires comparably detailed outcome information for those who were raised female and male. Currently, such information is unavailable. Nevertheless, full disclosure mandates that parents of infants born with essentially male genitalia be informed of the current status of outcome information while considering male in addition to female sex of rearing.

Regarding surgery, if being raised male is a viable option and/or if a portion of those raised females will develop a desire to be male, no external genital surgery should be done until gender identity has been reasonably established. If a male gender identity is clearly established, hypospadias repair, if needed, is all that would be needed to function throughout life as a male. A delayed surgery approach frees the family of the painstaking decision about the need for feminizing surgery by precluding removing a functional neurologically intact penis. A basic issue related to genital surgery among infants with intersex (DSD) is that genital tissue not be removed that can not be replaced if gender development occurs contrary to sex of rearing. This certainly applies if the outcome in such a child is male.

Gender reassignment surgery has become a valuable resource in improving QoL for transgender patients (12). For pediatric patients, especially infants with intersex genitalia, it provides a basis for parents to make difficult decisions since gender identity is still developing. Since

feminizing surgeries for patients with CAH historically have resulted in a high level of sexual dysphoria, it suggests the need for individual considerations for gender assignment. Because of critical tissue conservation, gender reassignment and alignment surgery in late adolescence or adulthood may be a better choice than during infancy.

The objective of the more specific outcome data is to prevent patients from having to undergo multiple gender reassignments or have a poor QoL outcome as a result of the feminizing surgery. It needs to be recognized that masculinization of the genitalia and the CNS can influence gender development and such needs to be recognized in outcome studies. Similar to transgender individuals, gender reassignment among these individuals should not be viewed as negative but as a positive step to improve quality of life. Assignment of these infants should not be based on karyotype, but must consider the extent of masculinization of the CNS and that effect on gender identity.

Fertility potential must be considered for these severely masculinized patients, regardless of sex assignment. While fertility among those born with Prader4/5 genitalia who were raised female continues to be potentially possible, it appears to be infrequent and may be related to the difficulty of suppressing androgen excess as well as the impact of androgen excess on body image and social relationships. Parenthood potential can be compared among those 46XX persons with CAH and Prader 4 or 5, transgender males, and females with long-term untreated PCOS (3). While germ cell retrieval assisted reproductive techniques (ART) may be unlikely given the exposure of the gonads to hormone that diminish retrieval of the germ cell, there may be surrogacy options. Similar to transgender individuals, these possibilities must be presented to parents as part of full disclosure.

Important for the care of these patients and families is psychological counseling initially and intermittently geared to level of understanding. An initial psychological assessment of parents as soon as possible after the birth of their child to identify their strengths and vulnerability (13). Throughout life, the need for psychological support must be evaluated periodically. Such would be included in the "good practices" approach (14). Ongoing psychological care should involve periodic discussions of such topics as cognitive and emotional responses and altered interpretations of religion or other cultural values. Outcome information must attempt to assess the impact of counseling or lack thereof. A basic tenant is that, if the parents and patient understand the pathophysiology of CAH in everyday terms, there will be motivation to treat as well as possible.

The limitation of this perspective is the lack of complete comparable outcome data for those individuals raised female versus male. This has been implied above together with the need for such published reports. Further, while it appears that those raised female born with severe masculinization have very low fertility rates or infertility,

it is unknown whether current medical care and surgical procedures will result in a better fertility outcome in the future. Moreover, the outcome in terms of QoL is not only multifaceted, while assessment testing procedures are lacking.

Individuals with CAH born with severely masculinized genitalia (Prader 4 or 5) appear to be at great risk for poor outcome impacting various aspects of QoL. Among individuals with CAH and a 46,XX karyotype, the occurrence of gender dysphoria may well be related to the degree of prenatal androgen excess evidenced by external genitalia masculinization and also postnatal androgen excess, resulting from lack of continual androgen suppression by glucocorticoid therapy. Currently available adult outcome data suggest that those 46, XX CAH patients raised male with essentially male genitalia may have a better adult outcome than those born with similar genitalia who were raised female including a clear gender identity and adult outcomes. Thus, until there are more complete adult outcome data among those raised female, male assignment should be considered as it may improve the chances for a higher QoL and to reduce the likelihood of adult gender dysphoria. Until gender identity becomes apparent, such individuals probably should have surgery deferred to preserve the potential for male sexual function and sensitive erotic tissue. Fertility potential if raised male is similar to that of transgender males.

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Authors' Contributions

C.P.H., P.A.L.; Have cared for patients with intersex disorders and contributed to this presentation including interpretation of publications, since 2006. U.B.; Provided a surgical and international perspective. C.L.J.; Provided

a theoretic approach. All authors read and approved the final manuscript.

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