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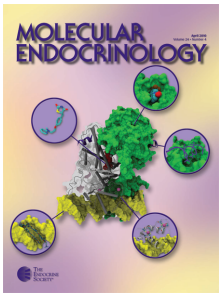

Approach to Assigning Gender in 46,XX Congenital Adrenal Hyperplasia with Male External Genitalia: Replacing Dogmatism with Pragmatism

Christopher P. Houk and Peter A. Lee

Department of Pediatrics (C.P.H.), Medical College of Georgia, Augusta, Georgia 30912; Section of Pediatric Endocrinology (P.A.L.), Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, Indiana 46202; and Department of Pediatrics (P.A.L.), Pennsylvania State College of Medicine, Hershey, Pennsylvania 17033-0850

The goal of sex assignment is to facilitate the best possible quality of life for the patient. Factors such as reproductive system development, sexual identity, sexual function, and fertility are important considerations in this regard. Although some DSD gender assignments are relatively straightforward, those with midstage genital ambiguity and unclear gonadal function represent a major challenge. A recent major change in DSD care has been to encourage a male assignment for 46,XY infants with ambiguous genitalia who have evidence of testicular function and *in utero* central nervous system androgen exposure. In contrast, assignment of virilized 46,XX DSD patients remains female when ovaries and internal organs are present, regardless of the extent of virilization of the external genitalia. In this paper, we propose consideration of male assignment for these 46,XX patients who have fully developed male genitalia based on available outcome data. **(*J Clin Endocrinol Metab* 95: 4501–4508, 2010)**

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- Become familiar with the factors to be considered in the infant requiring gender assignment.
- Be acquainted with guidelines for the clinical approach to infants with DSD based on clinical findings.

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A full-term newborn of a 24-yr-old primagravida mother was noted to have bilateral cryptorchidism. The delivery was uncomplicated, and the infant appeared healthy, weighing 3500 g and measuring 58 cm in length. Examination showed normal heavily pigmented male external genitalia with no palpable testes. Stretched phallic length was 3.5 cm [normal range for newborn male, 3.5 + 0.4 cm (1)], and prepuce and urethral meatal position were normal (Fig. 1A). Bilateral cryptorchidism was diagnosed. After circumcision and neonatal screening sampling on d 2 of life, the infant was discharged as a male.

He fed and slept normally and appeared healthy. On the eighth day of life, a positive newborn screen for

Abbreviations: CAH, Congenital adrenal hyperplasia; CAIS, complete androgen insensitivity; CNS, central nervous system; DSD, disorders of sex development.

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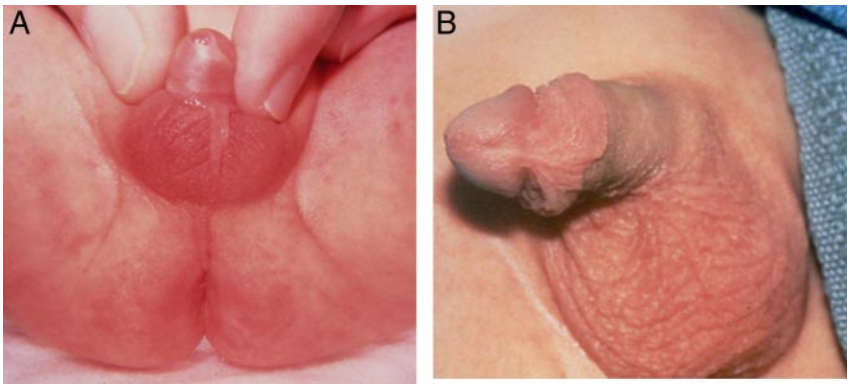

FIG. 1. Fully male genitalia of 46,XX CAH patients. A, External genitalia of a 46,XX neonate with fully developed male genitalia except for an empty scrotum. The scrotum is fully fused, and the urethral meatus is at the tip of the glans. A fully developed prepuce is intact. B, Genitalia of an older boy being raised male.

congenital adrenal hyperplasia (CAH) was reported; the 17-hydroxyprogesterone by fluoroimmunoassay was 6787 ng/dl (245 nmol/liter). Physical examination showed a well-hydrated male infant weighing 3275 g. Laboratory results showed the following: 46,XX karyotype; repeat 17-hydroxyprogesterone, above 10,000 ng/dl (>350 nmol/liter) (normal range for age, <77 ng/dl); androstenedione, 850 ng/dl (31.2 nmol/liter) (normal range, <279 ng/dl); testosterone, 176 ng/dl (6.1 nmol/liter) (normal female range, 64 ng/dl); 11-deoxycortisol, 190 ng/dl (5.5 nmol/liter) (normal range, 100 ng/dl); cortisol, 7 μg/dl (193 nmol/liter) (normal range, 2–14 μg/dl); sodium, 129 mmol/liter (normal, 136–145 mmol/liter); and potassium, 6.7 mmol/liter (normal range, 3.7–5.2 mmol/liter).

CAH 21-hydroxylase deficiency was diagnosed, and treatment with glucocorticoid, mineralocorticoid, and supplemental sodium was initiated. Abdominopelvic ultrasound demonstrated enlarged adrenal glands and a midline uterus. Retrograde urethrogram showed a penile urethra extending to the bladder without communication with the vagina. The parents met with a pediatric endocrinologist and discussed the pathophysiology, the diagnosis, and the treatment of CAH and the embryological development of internal and external genitalia, particularly noting the effect of excessive adrenal androgen on external genitalia in early fetal life.

Background

Many aspects of care for children with disorders of sex development (DSD), defined as a misalignment between chromosomal, gonadal, and phenotypic sex, have fundamentally changed recently—particularly regarding gender assignment. However, uneasiness persists about the management of children with DSD because of poor outcome. The three components of sexual psychosexual development—gender identity, gender role, and sexual orientation—may not always be concordant and aligned in individuals with DSD. However, in those with DSD, the primary goal is for gender identity to be consistent with gender assignment. In other words, an overarching goal of DSD management is to avoid a gender assignment that increases the risk of gender dysphoria.

In the past, similar discomfort led to the overly simplistic and dogmatic management approach, particularly gender assignment, whereby sexually ambiguous infants were assigned a gender based on a prescriptive set of rules. These rules involved potential for fertility and traditional sexual activity given possible surgical genital repair. For example, a 46,XY patient judged to have an inadequate penis was assigned female, whereas a virilized 46,XX patient with ovaries and a uterus was assigned female, independent of the degree of external genital virilization. To address the poor outcomes associated with the previous medical management paradigm, recent emphasis has been placed on the use of principles, cultural background, and parental input to help make clinical decisions in DSD infants—particularly those with uncertain outcomes regarding adult gender identity and quality of life variables.

Therefore, gender assignment in contemporary DSD management encourages consideration of multiple factors (Table 1), recognizing that some degree of gender predetermination may have taken place in some types of patients. Prioritization of impact must be made for each individual considering the following factors. Regarding gender assignment, etiology is the principal consideration when diagnosis-specific outcome evidence is available; the potential for adult fertility, parental support, and cultural factors are also paramount, particularly when outcome evidence is lacking. Although genital anatomy has been felt to be of limited value in determining outcomes (1) in ambiguous patients, we propose that genital development be given high priority for gender assignment when the external genitalia are entirely female or entirely male. All of the factors used to guide gender assignment must be considered in light of the considerable controversies that remain in this area. Most of these controversies flourish in the absence of reliable outcome studies and the tenuous understanding of the influences played by genetic, hormonal, and psychosocial factors on outcomes. In this paper, we focus on outcome and gender assignment of severely virilized 46,XX CAH patients.

TABLE 1. Factors to be considered for gender assignment

Probable adult gender identity
Deference to psychosocial factors when outcome unpredictable
Psychosocial factors
Family dynamics
Social circumstance
Cultural pressures
Fetal CNS androgen exposure
Specific diagnosis, if discernible
External genital development
Ambiguous, female, male
Surgical options for functional repair
Anticipated quality of sexual function
Ability to preserve neurovascular unit for sensitivity
Anatomy of postsurgical genitalia
Fertility potential
Assisted or unassisted
Presence of germ cells in ovarian or testicular tissue
Uterine and other Mullerian-derived internal female development
Male internal ductal and accessory gland development
Psychosocial risk for parents and individual
Acceptable assignment considering cultural/social situation
Inappropriate assignment leads to gender dysphoria
Separate gender identity from gender role and sexual orientation
Minimize physical risk
Gonadal cancer *vs.* preserving germ cells
Renal and urinary tract damage

Outcome information from 46,XX CAH patients with varying degrees of virilization who were reared female includes a report of 58 children who showed no dysphoria (2, 3), whereas another report found that five of 16 adults who had been reared female had gender dysphoria (4), suggesting that dysphoria may not become apparent until adulthood. Reports of 46,XX CAH patients initially assigned male but subsequently reassigned female (5–8) showed that four of 10 adult subjects had gender dysphoria. 46,XX CAH patients with male genitalia who were initially assigned male but were not reassigned female after the diagnosis included 35 subjects with 18 adults, including four who had dysphoria (5–9).

Outcome information remains inadequate to determine the adjustment and quality of life in those fully virilized 46,XX CAH patients regardless of gender assignment. However, we reported 10 adult 46,XX CAH subjects raised male, all of whom, despite adjustment problems often related to the lack of social support, had maintained a male gender identity and were sexually attracted to and reported satisfactory sexual intercourse with females (10). Therefore, in the absence of conclusive outcome data supporting the superiority of one gender assignment, we submit that a male gender assignment remains a viable consideration for fully masculinized 46,XX CAH patients.

This paper reviews these factors, highlighting considerations that we feel are important in gender assignment of highly virilized 46,XX CAH infants with essentially normal male external genitalia.

Shift in Perspective

A century ago, the primary determinant of gender assignment was gonadal differentiation; a half century ago, karyotype became the most important factor. These ideas were supplanted in the 1960s when the optimal gender approach was proposed as a way to improve outcomes. This approach based gender assignment on the potential for fertility, the ability to engage in traditional sexual activity, and the prevailing surgical limitations for genital repair. In retrospect, major shortcomings of the optimal gender approach stem from its failure to incorporate parental input into medical management, including gender assignment, and its dogmatic, inflexible approach. In addition, the potential for sexual activity was viewed from the limited perspective of an "adequate" penis, whereas the impact of surgery on adult female sexual sensitivity was not adequately considered.

Presently, in DSD patients lacking a specific etiological diagnosis, a composite of the factors (Table 1) felt to be important in adult outcomes is used to guide management. For example, for those with a 46,XX karyotype, ovarian differentiation, and moderate genital ambiguity, the most likely outcome and therefore gender assignment is female, as advocated a half century ago (11). In contrast, children with a 46,XY karyotype, testicular differentiation, and partially virilized external genitalia, the most likely outcome is a male gender, and a male gender assignment would likely be encouraged, an approach deviating significantly from previous recommendations. In cases with a 46,XY karyotype and completely female external genitalia [*i.e.* complete androgen insensitivity (CAIS), LH receptor mutation, testicular regression, SRY mutation, *etc.*], a female assignment is encouraged (12), an assignment made despite the presence of normally differentiated testes.

Our proposal is merely that the opposite situation be seriously considered; that is, a male gender assignment be considered for the 46,XX infant with male external genitalia. Although outcome evidence for this approach is incomplete, there are several lines of evidence that support it. First, although the incidence of gender dysphoria in completely virilized 46,XX patients raised male *vs.* female is unknown, there appears to be a high risk of gender dysphoria in those patients assigned female, regardless of karyotype (13). Additional, albeit indirect, support comes from the rarity of gender identity disorders and gender change in 46,XX DSD patients assigned male in infancy, including those who were diagnosed late and were not

reassigned female. Although four of 33 markedly virilized 46,XX CAH patients raised male were reported to have shown gender identity problems (8), there is no reported case of gender dysphoria so severe that the subject initiated a gender change to female. A single reference was identified that reported self-reassignment to female, which occurred in an individual with partial androgen insensitivity (14). In contrast, there are several reports of similar patients assigned female who self-reassigned to the male gender as adults. Additional support for a male assignment comes from evidence showing that the initial gender assignment remains the best predictor for adult gender identity in DSD patients (15). Therefore, in keeping with the more pragmatic approach currently supported by the medical community, we propose that a male assignment be considered in 46,XX DSD cases with male genitalia, when the parental input is supportive.

An additional benefit of male assignment is that it does not mandate the irrevocable loss of sensitive genital tissue. A male assignment therefore would offer more options for the adult DSD patient who would logically have a better outcome with surgical reassignment from male to female than vice versa. The male assignment also eliminates the risk of impaired genital sensitivity from feminizing genitoplasty. In addition, the proposal for less invasive surgery also aligns well with the message heard from patient advocate groups that propose limited surgery until the patient is old enough to consent. The recent Consensus Statement makes it clear that all gender reassignments must be patient initiated. With this in mind, we question whether feminizing genital surgery in the setting of a normal-appearing male genitalia is a form of sex reassignment?

Consensus Statement Recommendations

A primary motivation for the 2005 International Consensus Conference was to respond to the highly publicized reports of poor clinical outcomes of the optimal gender approach. It is important to recognize that the basis for most of the recommendations in this Consensus Statement (1) was implicitly tentative because of the low level of scientific support that underpins them, most being in the weakest category (expert opinion) Type II-2 (16, 17). It recommends an informed yet practical approach, individualizing recommendations based on known factors, and an open dialogue with an informed family and a multidisciplinary group. Because management of DSD children is uncertain, it is imperative that all decisions, particularly gender assignment, be made by a fully informed family and, once made, that subsequent reassignment only be initiated by the patient (1). Table 2 lists recommendations for gender assignment, but for most situations, data remain insufficient to make specific recommendations.

Family Involvement

The initial parent interview begins with reassurance that their DSD child can expect to have a fulfilling life, followed

TABLE 2. Gender assignment recommendations from Consensus Conference (1)

Assignment	Basis
1. Female	
CAIS (46,XY)	A. Female genitalia; all identify as female
Leydig cell agenesis (LH receptor defect) (46,XY)	No genital ambiguity
CAH (46,XX)	90% identify as female; inadequate data for those having complete male genitalia
2. Male	
5α-reductase deficiency	B. 70% identity as male
17β-hydroxysteroid dehydrogenase deficiency	~50% assigned female; self-reassign male
3. Base on gonadal, external and internal reproductive system differentiation	
Ovotesticular DSD	
Male	C. If functional testis and marked virilization
Female	If functional ovary and internal female development
Mixed gonadal dysgenesis	
4. Insufficient data for partial androgen insensitivity syndrome and cloacal exstrophy	
5. Generally those with 46,XY with evidence of testicular function, fetal CNS androgen exposure and some virilization; male	

TABLE 3. Guidelines for diagnostic approach

Physical findings	Possible diagnoses
1. Symmetrical male genital differentiation	A. Often unidentifiable etiology
Coronal or midshaft hypospadias	46,XY DSD, 46,XX DSD
Nonpalpable testes bilaterally	Rarely virilized 46,XX DSD (CAH)
2. Symmetrical female genital differentiation	B. 46,XY DSD
Palpable gonadal structures within labia	CAIS
	LH-receptor inactivating mutation
3. Symmetrical genitalia with	C. 46,XX DSD
Phallus > clitoral size	(Masculinized female)
Posterior fusion of labioscrotal folds	CAH, other placental, maternal or fetal causes
Fusion of labiourethral folds moving orifice	
Creation of urogenital sinus	
No palpable gonads within the labioscrotal folds	
4. Asymmetrical genitalia with	D. 46,XY DSD or sex chromosome DSD
Phallus with chordee, anchored ventrally	Partial or unilateral testicular differentiation
Single opening on perineum to phallic base	Mixed gonadal dysgenesis
Unilateral hemiscrotal structure	
Palpable gonad on ipsilateral side	
Labium on contralateral side containing no palpable structure	

by reviewing the information about their child's condition in an objective and realistic manner. These discussions should highlight the uncertainty associated with the differing expert opinions. Caution should be used to prevent the inadvertent introduction of bias through word choice, particularly the use of the karyotype as a type of hidden code indicating maleness or femaleness. If surgery is being considered, the complexity and number of surgeries should be presented, comparing, when pertinent, male and female reconstruction, being careful not to imply that surgery will solve all issues. Subsequent clinical information must be presented in a timely fashion. Ultimately, parents bear responsibility for decisions in DSD children, so it is imperative that their decisions be fully informed and then supported.

Patient Assessment and Management

The case presented is a patient in whom the specific diagnosis is known. When this is not known, a thorough evaluation is needed to make a specific diagnosis, if possible. This type of evaluation is thoroughly outlined by UpToDate.com (18).

Diagnostic approach

The initial evaluation involves a medical history noting familial disorders, a physical examination with particular attention to the genitalia, determination of karyotype, and, if findings are consistent with CAH, a rapid determination of 17-hydroxyprogesterone. Based on these findings, appropriate hormone levels including adrenal/gonadal steroid hormones, gonadotropins, or other factors should be ordered.

The initial physical examination notes genital symmetry, size, extent of fusion, orifice locations, and palpable gonads. Internal urinary-reproductive tract anatomy should be determined using appropriate procedures. Additional studies are based on individual physical findings such as palpable gonad(s) (Table 3). Karyotype is used in this context because it helps sort potential etiologies for a more intuitive diagnostic evaluation, but this should not lead one to the conclusion that it is of paramount importance in gender assignment.

Management

The management of patients with DSD is highly complex and beyond the scope of this article, which instead focuses on the situation exemplified in the case presentation. For more details on management, the reader is directed to UpToDate (19).

Gender Assignment Considerations

The basis for gender assignment in patients with DSD remains unclear. Searching for a single innate gender factor, such as gonadal differentiation or karyotype, risks overestimating the influence of neurobiological factors (13). Outcome studies, in fact, suggest that the best indicator of adult gender identity remains the initial gender assignment (13). Gender assignment recommendations (Table 3) are clear-cut in only a minority of DSD patients—typically, in patients without genital ambiguity who show an inconsistency between chromosomal, gonadal, or phenotypic sex. Examples are 46,XY patients with CAIS, LH receptor mutations, and those with sex reversal (46,XX testicular DSD and 46,XY complete gonadal dysgenesis). There is

uniform agreement that a female gender assignment is appropriate in instances with complete female genital differentiation (no masculinization), even when the karyotype is 46,XY and when the gonadal differentiation is more testicular than ovarian (1). Furthermore, in the instances of 46,XX testicular DSD with male external genital differentiation, it is agreed that the appropriate gender assignment is male despite the poor fertility.

Male gender assignment

There has been a shift toward male gender assignment in 46,XY DSD patients with poorly developed male genitalia, although the consensus recommendation for male assignment included only two specific diagnoses: 5α-reductase deficiency and 17β-hydroxysteroid dehydrogenase deficiency. This is a major departure from the optimal gender approach's recommendation that those with small penises be reassigned female. Most informed clinicians now recommend a male gender assignment for any virilized 46,XY patient with testicular function, even when the diagnosis is unknown. A basis for this shift comes from outcome information of undervirilized 46,XY patients who underwent feminizing surgery in infancy but nonetheless maintained a male gender identity (20).

Prenatal androgen exposure

The understanding of the effect of *in utero* androgens on human central nervous system (CNS) development remains inadequate to provide clear guidelines for gender assignment. But androgen-induced masculinization of the fetal brain does appear to be important in the DSD patient exposed to male typical levels of testosterone during fetal life, including virilized 46,XX DSD patients in whom such exposure produced male genitalia. The degree of fetal testosterone exposure is likely correlated with severity of CAH (21). This androgen effect has been documented in childhood sex-typed toy preferences, play activity, temperament, and playmate preferences (22). Its impact on gender identity and sexual orientation is unclear (23), although recent evidence suggests that bisexual/homosexual orientation may be correlated with prenatal androgen exposure plus masculinization of childhood behavior (24). High levels of fetal androgen exposure in the 46,XY infant with cloacal exstrophy are cited as a key argument for male gender assignment. We suggest that similar consideration be given to the 46,XX CAH child with functional male genitalia whose existence implies a high degree of masculinization of the brain.

Components considered for gender assignment

Table 1 suggests factors for consideration when a gender assignment must be made. If male assignment is considered, we feel that the presence of male genitalia, as opposed to ambiguous genitalia, should be considered as additional support for assignment. Given the high levels of fetal androgen exposure, we reason that a male adult gender identity is probable, or will at least be likely to be accepted, if male gender assignment is made.

Considerations for the 46,XX CAH patient with essentially male genitalia

The recommendation that all 46,XX CAH patients be reared female (1) fails to consider the unique challenge posed by the rare 46,XX CAH patient with essentially male genitalia. This recommendation may represent a persistence of the dogmatic approach for which the previous management paradigm erred. The consensus CAH statement (25) indicated that "there is insufficient evidence to support rearing a 46,XX infant at Prader 5 as a male," suggesting that with more evidence, the recommendation might change. Our recent experience and review of the literature (5, 6) support the viability of male assignment for such patients. Higher fetal androgen levels, normal male external genitalia, and being reared male all foster a male gender identity and, perhaps, a sexual attraction toward females (26). Adult male gender identity is apparent in such individuals, although the strong relationship between social and environmental support and overall adult adjustment is similar to that seen in other types of DSD.

Reconsideration of female assignment for all 46,XX CAH patients

In 1955, Lawson Wilkins noted that decisions of gender assignment were being made based "solely on the appearance of the external genitalia without further study" (27) and referred to "a grave error if the patient is a female hermaphrodite with congenital adrenal hyperplasia." His basis for this was that "cortisone in small doses" suppresses virilizing activity, and the patient will then "develop as a normal female and mature at puberty with ovulatory cycles." History has shown that this outcome is not certain.

Among women with CAH, the most severely masculinized subjects show the poorest ovarian function (28–31), and fertility tends to be more severely reduced (32–34). These patients also require the most extensive surgeries, and whereas newer surgical techniques promise better outcomes, it has not yet been documented whether these newer procedures improve the considerable dissatisfaction noted with cosmetic and functional outcomes (35).

There is no basis for considering male assignment for those with lower degrees of virilization (Prader 3 or less), although some adult 46,XX CAH female patients have

self- reassigned as male (36, 37). When compared with their less virilized CAH counterparts, studies of highly virilized CAH women show that fewer have had a spouse, partner, or sexual experiences with men (38), and more have sexual difficulties, decreased sexual activity, fewer personal relationships (39, 40), and a lower quality of life (27, 39). Although most are satisfied with the female gender, a significant percentage manifest a homosexual orientation, whereas typical male gender role interests and male-type childhood behavior are common (22). Although the incidence of sexual experience is lower in these women, the rates of bisexual/homosexual fantasy are higher than in controls (30). This is consistent with a relationship between androgen exposure and sexual orientation (24).

When the basic factors for gender assignment (Table 1) are applied to the 46,XX CAH patient with essentially male genitalia, the male external genitalia, the prenatal CNS androgen exposure, the masculine physique, and capability of satisfactory adult sexual function all make compelling arguments for male assignment when parents support it.

Basic principles that should be considered in decision making are to attempt to provide for fertility and sexual relations while minimizing health and psychosocial risks (41). However, if male sex of rearing is chosen for the 46,XX CAH patient, retention of internal female reproductive structures and ovaries until puberty risks development of gynecomastia and withdrawal bleeding (cyclic hematuria). Parents should be informed of the options to preserve fertility, including the remote, although theoretically possible, ability to harvest and preserve ova. It must be realized that in any one individual it is probably impossible to adhere to all of the principles and still make the best possible decision. Basic care guidelines include the critical need of psychological care, ongoing open communication, and mandatory parental participation for optimizing outcomes with the realization of the importance of family substrate for good outcomes.

For the case report presented, parents mandated a male sex of rearing for their infant. They have been compliant with the medical recommendations for managing his CAH and have supported his male sex of rearing. Currently, this boy has well-developed genitalia (Fig. 1B), is approaching the age of puberty with apparent well-established male identity, and is involved in sports and other typical male activities. His parents realize that outcome is not yet fully realized. The lack of outcome data is clear, and studies and reports expanding such are sorely needed. To verify outcome data, it would be helpful if those caring for such patients could work with others using similar outcome measures.

In summary, the approach to the child born with DSD is multifaceted. The recent consensus conference offered laudable guidance on many of the issues faced by the practitioner caring for these children. One guideline endorses the parents' rights to make treatment decisions about their children, particularly in cases where outcomes are uncertain. Although there is no basis to challenge the gender assignment for 46,XX CAH patients with genital ambiguity, it is our feeling that 46,XX CAH patients with nearly normal male genitalia are in a setting where the outcome is uncertain. We do not suggest that all highly virilized 46,XX CAH patients be assigned male, but simply that male assignment be considered. It has been our experience that many of the children's families find it counterintuitive that female assignment be suggested for their newly born "boy" and that our consent for male assignment merely acknowledges their position. We, the medical care team, should be bold enough to consider the merits of this decision and learn from it.

Acknowledgments

Address all correspondence and requests for reprints to: Peter A. Lee, M.D., Ph.D., Department of Pediatrics, MC-H085, Pennsylvania State College of Medicine, The Milton S. Hershey Medical Center, P.O. Box 850, 500 University Drive, Hershey, Pennsylvania 17033-0850. E-mail: plee@psu.edu.

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