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Assignment of the sex of rearing in the neonate with a disorder of sex development

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Abstract

Purpose of review—Infants born with ambiguous genitalia [henceforth referred to as Disorder of Sex Development (DSD)] present a unique set of clinical challenges requiring an organized yet practical approach. Given the low frequency with which these types of patients are encountered, their management is best accomplished by practitioners experienced with DSDs. The goal is to discuss, in light of recent publications, information required to make rational management decisions and provide our perspective.

Recent findings—An overview of DSD with recent publications germane to diagnosis, management, and sex of rearing decisions is presented. Most DSD etiologies are rare and outcome studies are scarce. A high degree of uncertainty and low level of scientific support have led to most of the controversies in this field.

Summary—Care of a DSD infant must be individualized. Management decisions are based on multiple factors including reproductive anatomy, DSD etiology, parental/cultural factors, and most importantly outcome. Parents should be provided with an objective, realistic, and complete assessment of their child's condition including a discussion of the level of uncertainty (regarding outcome) inherent in each individual case. The medical care team must strike a balance between presenting available outcome data and differing opinions on DSD management in helping parents reach management decisions, particularly concerning sex of rearing.

Keywords

ambiguous genitalia; disorders of sex development; sex of rearing

Introduction

The approach to sex of rearing decisions in DSD patients has changed fundamentally over time. DSD patients have been a quandary to humans since ancient history, attested to by the

Greco-Roman mythological character Hermaphroditus. A tendency of discomfort/repugnance to genital ambiguity continues to create barriers for their management, within the healthcare team as well as for the family and friends of the affected children. Although our approach continues to evolve, even in modern times DSDs continue to present a problem, in part because of cultural factors [1]. At one time, gonadal histology (testicular or ovarian) was thought to indicate the true sex/gender. Subsequently, sex chromosomes also became a major factor in identifying the true sex/gender. Eventually, the ability to surgically create sexually functional genitalia became a dominant factor in decision-making. Contemporary management sees DSD decision-making as multifaceted, involving many factors (none to the exclusion of the others), including etiology and most likely gender outcome.

Background

The Consensus conference on Management of Intersex Disorders held in 2005 was a response to the need to assess the care of these patients [2], in large part because of severe complaints from patient advocacy groups. The previous prevailing medical approach, called the optimal gender approach, was based on publications and recommendations of the premier sexologist, Dr John Money. One radical practice stemming from Dr Money's approach was the recommendation that children with penises judged to be too small for intercourse be reassigned female, an approach applied to 46,XY DSD patients (including those with cloacal exstrophy and panhypopituitarism). Intense ongoing psychological counseling was usually absent, although consistent parental support, particularly maternal, was felt to be critical for the patient to assimilate the gender assignment. Because of dramatic failures, the optimal gender approach has been greatly criticized but not systematically reviewed.

Although the recent consensus statement has made a valiant attempt to demystify DSD management, it, in fact, asks many more questions than it answers. These recommendations should not be cited as definitive because of low levels of scientific support. Most DSD etiologies are rare and outcome studies are scarce; hence, evidence used to develop recommendations for DSD management is type II, the weakest category (expert opinion) [3,4]. Some may have been overreactions to the defects in the optimal gender approach, which may create outcomes of another extreme. This possibility leaves the physician responsible for caring for the DSD infant in a difficult position, forcing open dialogue in the multidisciplinary group caring for DSD patients and the need to base every DSD child's management on many factors. Given these limitations and the underlying uncertainty over our management of DSD children, it is as important as ever that decisions about sex of rearing be made by a genuinely informed family.

Recent literature illustrates the dangers of using the 2006 Consensus statement as the only guideline when caring for DSD patients. We need to try to avoid allowing the pendulum concerning sex assignment to swing too far and the future outcry from patients to come from a different perspective.

Diagnostic approach

The diagnostic approach to DSD patients begins with a complete karyotype, followed by additional studies on the basis of individual circumstances such as physical appearance (Table 1). A recent publication reviews diagnosis and treatment of 46,XY DSDs [5•].

Sex assignment considerations

The 2006 Consensus Statement on the Management of Intersex Disorders recommendations on sex assignment decisions were based on very limited data. Indeed, the only clear recommendation was for a diagnosis not presenting with genital ambiguity for which no management controversies exist: female with the complete androgen insensitivity syndrome (cAIS). This could also apply to patients having essentially female or male genitalia, such as those with luteinizing hormone receptor mutations (Leydig cell agenesis) and sex reversal (46,XX testicular DSD or 46,XY complete gonadal dysgenesis).

As approximately 70% of 5 α reductase deficiency patients may identify as male in adulthood and approximately 50% of 17 β hydroxysteroid dehydrogenase deficiency patients assigned female may self-reassign to the male gender in adulthood, it was recommended that a male sex of rearing should be considered for these diagnoses.

The consensus statement position that all 46,XX congenital adrenal hyperplasia (CAH) patients be raised as female was based on the logic that 90% of 46,XX CAH patients identify as females and there are little outcome data for those patients raised as male. Although the statement reads ‘evidence supports the current recommendation to raise markedly virilized 46,XX infants with CAH as female’ [4], it references a former consensus CAH statement [6], which states that ‘there is insufficient evidence to support rearing a 46,XX infant at Prader 5 as a male’. Hence, a recommendation should not include 46,XX patients with essentially complete or fully masculinized genitalia (Prader 4 or 5). The recommendation should be applied to those with Prader 1 through 3 genitalia. A summary of outcome data [7•] suggests that, when the diagnosis is delayed and androgens are not suppressed during childhood, gender identity may gradually change from female to male.

Component of gender make-up can be listed as follows:

1. Gender identity
 - a. The internal sense of being male or female
 - b. A person’s concept of self as being male or female, masculine or feminine, or rarely ambivalent
 - c. Generally attained during infancy and reinforced during childhood and adolescence
 - d. For purposes of this review, gender identity had been used rather than sexual identity because of the inclusion of sexual orientation into the latter
2. Gender role

- a. Behavior viewed as masculine, feminine or neuter within a particular culture or society
 - b. Characteristics that are sexually dimorphic within a population
 - c. Gender role behavior may express non-conformity
3. Sexual orientation
- a. Direction of erotic attraction toward the opposite, the same or both sexes
 - b. Includes behavior, fantasies and attractions
 - c. May not be focused until puberty or after
4. Gender dysphoria
- a. Dissatisfaction with one's gender (masculine or feminine) because of conflict with one's physical development; discontent with biological sex
5. Sexual identity
- a. Often implies a combination of how a person identifies (gender identity) and sexual orientation

A recent report from India includes seven 46,XX CAH patients raised as males because of family preference, older age of diagnosis and having a 'good' phallus [8•]. A 46,XX CAH patient with Prader 3 genitalia who has chosen to live as a monogamous heterosexual male was also recently reported [9•]. These patients should be reminders of the unknown concerning gender makeup and behave an open approach, rather than citing the consensus statement recommendation [10]. Male sex of rearing should not be precluded for those with Prader 4 or 5 genitalia. General guidelines for assessment should be applied to them until more outcome data are available. Although we do not disagree that most 46XX CAH patients should be raised in the female gender, we do not feel there is sufficient evidence for the extremely virilized patients and suggest individualized counseling.

For those with ovotesticular DSD, the 2006 Consensus recommended that assistance techniques for potential fertility be considered with sex assigned according to reasonable potential for fertility. Those with a potentially functional ovary and Müllerian duct-derived structures should be raised female, or, if functional testes were present together with marked virilization, as male. Such an approach is consistent with this opinion paper and also closely resembles that proposed by John Money in the Optimal Gender approach.

The consensus found inadequate data for a basis of sex assignment recommendation for the remaining diagnoses, including the partial androgen insensitivity syndrome, a situation that has led to considerable dissatisfaction when feminizing surgery occurred in a person who developed a male gender identity [7••], and cloacal exstrophy, a situation in which outcome data are unclear. Again, it is important that the other extreme, for example, raising all 46,XY cloacal exstrophy patients as male, not become the current routine, because it may lead to as much dysfunction as the previous practice of reassigning all as female.

The assignment among those diagnosed with partial androgen insensitivity syndrome, often made without genetic verification, falls into that general category in which numerous factors must be considered. Because time is needed to determine long-term outcome, extreme caution must be used with revelation of possibly diminished sensitivity and functionality of surgically constructed genitalia. One individual rejected female assignment and self-reassigned male at 10 years of age, had a phalloplasty, is awaiting a penile implant and expresses satisfaction [7••].

Two general recommendations in the consensus statement were that children with a DSD and an XY karyotype should be raised as male if there is evidence of androgen responsiveness, including phallic development, or as female if the potential for androgen responsiveness is lacking (as in cAIS), and, for fully masculinized individuals with an XX karyotype who are identified later in life, that no consideration of gender reassignment be given unless initiated by the patient and only after careful psychological evaluation.

Although the consensus statement terminology of ‘disorder of sex development’ and the newer classification scheme avoid many of the negative terms employed by previous classifications, other recommendations should be used on the basis of the strength of the data used to formulate them, which is usually poor, resting only on expert opinion. The major impact of the 2006 consensus statement should be the overwhelming need for further information [11]. Broad recommendations for heterogeneous conditions such as XY,DSD are meaningless. When pathophysiology becomes better understood, clearer recommendations can be made.

Available outcome data published since the consensus conference show:

1. Many patients fare well and are leading productive lives, whereas gender dysphoria has been underestimated in the past [7••]. This emphasizes the need for gender and sexual counseling as part of the continuing care of these individuals.
2. A contribution of socialization/learning to psychosexual development – there is evidence that masculinity and femininity proceed along female or male-typical patterns depending on sex of rearing. Masculinity and femininity assessed by a self-reported questionnaire in 40 adults with 46,XY DSD found higher masculinity and lower femininity scores in those reared as male and higher femininity and lower masculinity for those raised as female [12•].
3. Postconsensus clinical approach – in Norway [13] 10–12 DSD children are born annually who require sex assignment and for whom a precise diagnosis is not always possible, making factors such as physical development, hormones, genetic studies, the impact of prenatal CNS androgen exposure and parental input upon psychosexual development pertinent, with the realization that DSD children will not necessarily develop a gender identity consistent with the assigned sex.
4. Culture mandates a persistence of the traditional approach – a report from India, probably as a manifestation of the impact of ‘socio-cultural compulsions’, appears to continue to use the traditional approach to gender assignment [8•]. An algorithm uses a ‘good phallus’ before or after hCG stimulation as the criteria for male

assignment in 46,XY DSD and sex chromosomes DSD (formerly true hermaphroditism), whereas a 'negligible' or small phallus is the basis for assigning female. The danger of such guidelines and algorithms is oversimplification and hence they cannot often be used for DSD management. Chromosomal sex has no role to play, whereas gonads, internal and external genitalia, together with phallic size, appear to be primary factors in sex assignment in India.

5. Impact of genital anatomy and surgical reconstruction on psychosexual development – questionnaires concerning penile self-perception, gender-role behavior, sexual experiences and sexual attitudes in 68 7–17-year-old males, postsurgical for hypospadias (two thirds with glanular or coronal forms), were similar to 68 control boys [14•]. Although hypospadias can be considered a form of DSD, the impact of minor deviations in genitalia may be less than those seen in individuals with more pervasive ambiguity.

These publications relate to some of the numerous factors to be considered for sex assignment. A complete diagnostic evaluation includes a physical examination and laboratory and imaging studies. Physical findings must include a description and symmetry of the external genital development including degree of virilization, Prader staging (as has been listed above) and the presence and position of gonads. Asymmetry is primarily a result of greater virilization of the labioscrotal fold-derived structures on one side than the other, commonly so that one side appears more like a labial fold and the other like a hemi-scrotum.

The bases for determining gender assignment include specific diagnosis if possible, genital anatomy, surgical options, potential for fertility (the presence of germ cells within the gonads), the potential for adult sexual responsiveness/function (not necessarily limited to intercourse), and, when available, factors that may predict the most likely adult gender identity. For underdeveloped male genitalia, the capacity to respond to exogenous androgen may not be a practical method for determining gender assignment. Sex of rearing should be assigned as soon after birth as attainable information is gathered, usually within a few days. In no instance should lack of assignment persist beyond the first few weeks of life.

Parental backgrounds and expectations, broader family dynamics, social circumstance, and ethnic or cultural influences must be considered. A gender assignment should always be made, while there may be instances in which the family decides to delay surgery until the child is considered old enough to decide upon surgery. Currently, such a delay is not recommended for the child with severely ambiguous genitalia.

Assessment considerations

Evaluation of the DSD patient must involve surgical options, impact of fetal androgen exposure, potential for adult sexual function, psychological and cultural considerations.

Surgical options

It is recognized that previous genital surgery was often unsuccessful in regards to acceptable cosmetic outcomes and sexual function. This has resulted in intense controversy over the need for surgery, particularly in infancy [7•]. However, current surgical techniques should

permit improvements in the ability to reconstruct genital anatomy while preserving the neurovascular supply and the clitoral erectile mechanism.

The 2006 consensus statement recommendations concerning surgery include no surgery for modest clitoral hypertrophy, early vaginoplasty and clitoroplasty as an appropriate choice in children with a high proximal junction between the vagina and urethra, if it can be performed at a center with large experience, and consideration of gonadal removal in those with risk of malignancy [4].

In-utero androgen exposure upon CNS development

Our knowledge of the impact of androgens upon the human CNS *in utero* is insufficient to provide clear guidelines. Not only is the time frame of in-utero androgen exposure unknown; the relative contribution of social/environmental factors in determining sexual behaviors remains unclear and likely varies in each individual. Although there appears to be an influence on cognitive function and ‘typical gender-related’ behavior, the impact on gender identity and sexual orientation is unclear. Hence, the weight assigned to this variable may depend on other findings (micropenis, exstrophy of bladder, mixed gonadal dysgenesis, ovotesticular DSD, aphallia). Examples of the challenges encountered with sex of rearing where male levels of fetal androgens exposure have occurred include the 46,XY child with normal testicular development but underdeveloped or absent penis, the 46,XX child with severe adrenal hyperplasia and markedly masculinized external genitalia, and the 46,XY patient with bladder exstrophy.

Potential for adult sexual function

It is unclear what relative weight should be placed on a ‘functional penis’. Because it is now generally accepted that 46,XY patients with micropenis and evidence of inutero androgen exposure have better outcomes with a male gender assignment, it would seem that little weight should be placed on this factor, particularly if functional testes are present. Male assignment is appropriate for the individual having a fully innervated, albeit small, penis, although this is not clear for the aphallic 46,XY patient.

Parental perspective

The sex of rearing decision is the parents’ right, obligation, and responsibility. The medical care team’s primary role is to evaluate the patient and inform the parents as completely as possible about the diagnosis, possible therapies, available outcome data, support groups, and sources of second opinions. An aim of the initial interaction with the parents is to encourage them to challenge the traditional concepts of completely distinct male or female development and encourage them to view sexual features and gender as existing along a continuum, giving them the option to see their child as something other than a ‘freak’, while giving them hope for a well adjusted child. An understanding of basic embryology, an appreciation of variation of development in the biological world and a realization of how masculinity and femininity overlap and change with cultures and over time should provide a basis to endorse the concept of a continuum.

Cultural considerations

It is clear that attitudes concerning gender and sexuality, including acceptance of intersexuality, differ significantly between various cultures [3]. Furthermore, until now it can be said that the medical approach to intersexuality has been guided more by cultural bias than by objective medical criteria. Although criteria and recommendation for the most appropriate sex assignment involve genetic, biochemical and clinical findings, cultural factors, education and society play a major role in the outcome of such assignments.

The management of DSD in different cultures is a consequence of traditional beliefs, folk remedies, prejudices, fostered by rumor and discrimination, and resources for healthcare [15•]. However, it is useful to remember that persons with DSDs desire the same things in life as everyone else, namely to find someone who will love them, to be valued as a human being, to feel at home in their bodies, to be able to have satisfactory sexual relations when desired, to be integrated into their general community, and to be able to trust their medical caregivers. Hence, the framework for decision-making outlined as follows, which is based on ethical principles, can be universally applicable, regardless of the cultural and social situation [14•]:

1. Keeping physical risk at a minimum
 - a. Risk of gonadal cancer (those with Y chromosome and gonadal dysgenesis)
 - b. Osteoporosis (lack of hormonal replacement for hypogonadal state)
 - c. Adrenal crisis (among those with most forms of adrenal hyperplasia)
 - d. Urinary tract infection/outflow obstruction (genital anatomic defects)
2. Keeping psycho-social risk at a minimum
 - a. Gender dysphoria as a consequence of inappropriate sex assignment
 - b. Making child acceptable to parents, enhancing bonding
 - c. Education to avoid social/cultural disadvantage
 - d. Avoid social isolation, distress, embarrassment (having different genitalia)
3. Preserving potential for fertility
 - a. Maintaining gonads containing germ cells
 - b. Using available fertility preservation techniques
 - c. Utilizing existing structures if in-utero pregnancy potentially possible
4. Preserving or enhancing capacity for satisfying sexual relations
 - a. Avoid removal of sensory neural vascular supply to genitalia
 - b. Utilize existing genital structures even though ideal structures are impossible
 - c. Use best existing surgical techniques

5. Leaving, when possible, options for the future (not removing gonadal and genital tissue)

Psychological considerations

The quality of life of DSD patients, particularly women with CAH, has been impaired by psychosexual difficulties [7•]. Although psychosexual differentiation has traditionally been described in three components of sexual development (as has been listed above) (gender identity, gender role, and sexual orientation) for the DSD patient, gender identity is of primary importance since gender role varies with time and cultures, and sexual orientation cannot be considered a bad outcome. The goal would be for gender identity to develop consistently with sex of rearing. Ongoing psychological counseling should be helpful in this regard; unfortunately there is a paucity of experienced counselors and there are no recent guidelines. It is important that likely the major problem for patients with cAIS in the past was the failure of full disclosure to the parents and patient, a situation which understandably led to considerable anger and resentment [7•].

It is important to realize that significant psychosexual issues will persist for the lifetime of the DSD individual born with genitalia requiring a decision concerning sex of rearing and that no single specific care plan/approach/set of guidelines can be applicable to all individuals. Further, adjustment and quality of life issues will vary and depend upon numerous factors, some of which may be uncontrollable. Gender role behavior for the female CAH patient is usually affected during childhood, sexual orientation is more often bisexual or homosexual, but gender identity is usually not affected [7•].

A summary report [16•] of sexual orientation in women with CAH of increased bisexuality and homosexuality also includes new information from 143 CAH women, including 82 with nonclassical form, and 24 control women. Although most CAH women were heterosexual, both bisexuality and homosexuality were increased above controls, even among the nonclassical, but this correlated with the degree of prenatal androgenization. Bisexual or homosexual orientation correlated with masculinization measures of nonsexual behavior and was predicted by both prenatal androgenization and masculinization during childhood. Because these data support a relationship between sexual orientation and prenatal androgens, this information should be considered in future deliberations concerning sex of rearing.

Conclusion

The practice of deciding the better sex of assignment for the DSD child is based upon which gender that child best fits considering functionality, pubertal and adult development and fertility. Also, the traditional positions must be flexible enough to be open to new information and dogma. For example, the main argument used that all 46,XX CAH patients should be raised as female because of the potential for fertility may be too narrow, as, indeed, may be the argument that a genetic male with too small a phallus should be raised as a female.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 559–560).

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Table 1

Diagnostic evaluation and potential diagnoses based upon symmetry of genitalia

Symmetrical external genitalia
Palpable gonad
Gene testing SF-1
Nonpalpable gonad
Ultrasound
Uterus (lack of MIH)
Congenital adrenal hyperplasia
In-utero androgen exposure
Hormonal assessment
17 α -Hydroxyprogesterone
Androstenedione
Testosterone
Plasma renin activity
No uterus (presence of MIH)
Leydig cell hypoplasia
3 β -HSD
17 β -HSD
Androgen insensitivity
5 α -Reductase deficiency
Testicular regression
Hormonal assessment
MIH
LH
Testosterone
FSH
Inhibin B
Androstenedione
Asymmetric external genitalia (virilization of labia different on each side)
Assessment
FISH (fluorescence <i>in situ</i> hybridization) for SRY
Hormonal assessment
MIH
LH
Testosterone
FSH
Inhibin B
Androstenedione
Gene testing
SOX9 – Gonadal dysgenesis
WT1 – XX Male (+SRY)

DAX1 – XY Female (–SRY)

WNT4 – XO/XY

DHH – Ovotesticular DSD

ATR

SLOS

Imaging

Ultrasound

FSH, follicle-stimulating hormone; HSD, hydroxysteroid dehydrogenase; LH, luteinizing hormone; MIH, Müllerian inhibiting hormone; SRY, sex-determining region Y.