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Fluidity models in ancient Greece and current practices of sex assignment

Min-Jye Chen, MD^{a,1}, Bonnie McCann-Crosby, MD^{a,*}, Sheila Gunn, MD^a, Paraskevi Georgiadis, MD^b, Frank Placencia, MD^b, David Mann, MD^c, Marni Axelrad, PhD^d, L.P. Karaviti, MD, PhD^{a,2}, and Laurence B. McCullough, PhD^{e,2}

^aDivision of Pediatric Endocrinology, Baylor College of Medicine, Texas Children's Hospital, 6701 Fannin Street, Suite 1020, Houston, TX 77030

^bSection of Neonatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX

^cDepartment of Anesthesiology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX

^dSection of Psychology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX

^eCenter for Medical Ethics and Health Policy, Baylor College of Medicine, Houston, TX

Abstract

Disorders of sexual differentiation such as androgen insensitivity and gonadal dysgenesis can involve an intrinsic fluidity at different levels, from the anatomical and biological to the social (gender) that must be considered in the context of social constraints. Sex assignment models based on George Engel's biopsychosocial aspects model of biology accept fluidity of gender as a central concept and therefore help establish expectations within the uncertainty of sex assignment and anticipate potential changes. The biology underlying the fluidity inherent to these disorders should be presented to parents at diagnosis, an approach that the gender medicine field should embrace as good practice. Greek mythology provides many accepted archetypes of change, and the ancient Greek appreciation of metamorphosis can be used as context with these patients. Our goal is to inform expertise and optimal approaches, knowing that this fluidity may eventually necessitate sex reassignment. Physicians should provide sex assignment education based on different components of sexual differentiation, prepare parents for future hormone-triggered changes in their children, and establish a sex-assignment algorithm.

Keywords

DSB; Sex Assignment; Androgen Insensitivity Syndrome; 5-alpha reductase deficiency; Gonadal dysgenesis

*Corresponding author, mccann@bcm.edu (B. McCann-Crosby).

¹Dr. Chen and Dr. McCann-Crosby: First coauthors, equal contributions.

²Dr. L.P. Karaviti and Dr. McCullough: Senior Coauthors, equal contributions.

Introduction

Patients with disorders of sexual development (DSD) present unique challenges with respect to sex assignment, parental education, and medical management. Many of these patients are diagnosed in infancy because of ambiguous genitalia that prompts immediate evaluation, although some patients with DSD are diagnosed later in life.

Fluidity of sex is built into human biology. In early fetal development, the gonads are bipotential (Fig. 1), and specific pathways lead to gonadal differentiation into either ovaries or testes and to the differentiation of the external genitalia. When the two differentiation pathways are conflated because of atypical developmental signals, the result can be anatomically ambiguous genitalia and atypical gonads at birth. In this context, the usually straightforward issue of sex assignment becomes complex and can be a changeable process, especially at the critical developmental stage of puberty. Although sex assignment is often made in the newborn period, under certain conditions, this assignment may be altered as children age and progress through puberty.

This potential for fluidity in DSDs and possibility of metamorphosis at a later developmental stage require greater understanding from both the biological and psychological perspectives. For the biological perspective, continued knowledge acquisition about the biological changes in the gonads, external genitalia, and the brain will inform practice. For the psychological perspective, we can look to positive models of cultural attitudes about these conditions, going as far back as the ancient Greeks as a source. What do ancient Greek art and history reveal about metamorphosis and resultant fluidity of sex and gender? Mythological figures such as Hermaphroditus and Daphne provide positive models of physical metamorphosis, fluidity, and empowerment. This model can serve as a positive approach to caring for patients with disorders of sexual development. Here, we examine the potential for fluidity in sex assignment associated with three clinical entities. As we examine positive approaches and take ancient Greek models as a basis, we hope to provide education for providers and families to de-stigmatize potential changes in sex assignment.

Three conditions associated with fluidity and possible metamorphosis

Three entities are associated with the sort of fluidity that can lead to a later metamorphosis—a change from one sex assignment to another. These conditions are androgen insensitivity syndrome (AIS), 5- α reductase deficiency (5ARD), and gonadal dysgenesis. In these cases, it is important to educate families about the potential for shifting sex assignment to better prepare them for the uncertainty that may lie ahead and to embrace the change.

Androgen insensitivity syndrome

Androgen insensitivity syndrome (AIS) is the most common undervirilization syndrome among XY disorders of sexual development.¹ The syndrome is caused by inactivating mutations in the androgen receptor, leading to androgen resistance. There is wide phenotypic heterogeneity depending on the degree of this resistance. AIS can be categorized as complete (CAIS), partial (PAIS), or mild (MAIS), this last of which involves minor findings such as infertility without major changes in the external genitalia.²

Classically, a person with CAIS presents as a phenotypic female with sparse or absent pubic and axillary hair. Patients typically are identified in infancy by the presence of inguinal hernias or in adolescence because of primary amenorrhea. PAIS presentation is more variable; patients may be identified as part of evaluation for ambiguous genitalia at birth, with an appearance that can range from undervirilized male to virilized female with clitoromegaly. MAIS patients are typically phenotypically male and may be identified as late as adulthood as part of an evaluation for male infertility.^{2,3}

5- α Reductase deficiency

5ARD is a rare male undervirilization syndrome due to an alteration in the 5- α reductase gene *SRD5A2*. Mutations in this gene cause decreased activity in 5- α reductase type 2, which leads to impaired conversion of testosterone to the more active metabolite dihydrotestosterone, which has a higher affinity for the human androgen receptor and plays the dominant role in fetal development of the male external genitalia.⁴ The general prevalence of 5ARD is unknown, but relatively higher prevalences have been reported in certain populations, including in the Dominican Republic, Turkey, Mexico, Brazil, and the Gaza strip.⁵

Classically, patients with severe 5ARD have normal-appearing female genitalia at birth, with virilization and development of male secondary sexual characteristics at puberty. However, phenotypic variability ranges from normal female-appearing genitalia to clitoromegaly to microphallus with hypospadias to isolated micropenis, although most patients present with severe ambiguity. There is a lack of phenotype–genotype correlation.^{5,6}

Gonadal dysgenesis

In gonadal dysgenesis, abnormal gonadal development (ovarian or testicular) arises because of mutations in genes involved in gonadal differentiation or numerical or structural anomalies related to the sex chromosomes.⁷ In complete XY gonadal dysgenesis (Swyer syndrome), testicular development is absent, leading to a female phenotype. Patients with complete gonadal dysgenesis present only in the adolescent period because of a lack of menarche and breast development. Patients who have XY partial gonadal dysgenesis (PGD) have varying degrees of virilization of the external genitalia depending on the degree of testicular function. The most common karyotype in patients with XY PGD is 45,X/46,XY, as also seen in mosaic Turner syndrome. Phenotypes can range from completely female with Turner syndrome features to an ambiguous, undervirilized male to a normal phenotypic male.⁸

Current issues

Within the context of managing sex assignment in individuals with these conditions and the potential for that assignment to change with the metamorphosis of puberty, several areas require attention. First, clinicians need to establish an understanding of how these conditions present at birth and the different paths they may take at puberty. Second, with the current understanding, it is largely not possible to predict these paths, so there is a need to determine how to create a reliable, workable assignment of sex and gender when uncertainty and resulting fluidity of sex and gender cannot be eliminated.

Regardless of these factors, clinicians must understand the nature of fluidity in its biological, psychological, and social components associated with it, so that they can communicate this information to families in a timely way to prepare them for upcoming possibilities. Ultimately, it will be critical to understand these changes not only for the genitalia and gonads but also for the brain so that we better inform positive practices when it comes to assigning sex, taking both the biological and psychological perspectives into account. For the latter, we perhaps need look no further than some well-known examples from the ancient Greeks. This is of more than mere antiquarian interest; there are clinically applicable lessons to be learned from our ancient forebearers.

Fluidity in ancient Greece: Models for a modern approach

What do ancient Greek art and history reveal about metamorphosis? Mythological figures such as Hermaphroditus and Daphne provide positive models of physical metamorphosis as fluid and empowering. These models can inform and support positive approaches to caring for patients with DSD.

In ancient Greece, individuals with DSD or the potential to metamorphose or exhibit role fluidity were celebrated and part of the fabric of the society. This societal inclusion translated into psychological and social acceptance of these roles as a part of the sociocultural constructs of the population. In our modern medical community, when we carry out sex assignment for individuals who have the potential to metamorphose given their biology, we must consider modern psychosocial constraints in addition to medical and psychological support. Taking the origins of acceptance from the examples of ancient Greece, adjusted to today's social standards, is one avenue to reach patients and families with a message of positivity about fluidity.

The Greek models

Two Greek figures in particular represent these positive social attitudes around sex assignment fluidity. The first is Hermaphroditus, son of Aphrodite (Roman Venus), the Greek goddess of love, and Hermes, the messenger of the gods (Roman Mercury). Hermaphroditus (Fig. 2) was one of the love gods, usually depicted with wings on his head and as a female figure with male genitalia. In Greco-Roman art, he represents androgyny, and his story provides a model of empowerment for those who are anticipating physical and cultural bipotential sexuality, or existence in multiple forms.

Daphne, who was a reluctant love interest for the god Apollo, represents the pubertal tensions of innocence and lust. She serves as a model for having a positive attitude about metamorphosis, ending her story as a forever green and flourishing laurel tree. Daphne and her story represent the core idea of the power of transformation, which is accepted in her narrative as a fully positive phenomenon, a principle that is key for this patient population.

Hermaphroditus: A model of empowerment

Examples of Hermaphroditus representing empowerment in metamorphosis abound in Greek art, from one of the oldest works—a painting on a vase showing him as a winged

youth with female hair, breasts, and thighs but male genitalia—to later Greek and Roman frescoes depicting a similar mix of traits. The sheer number of surviving examples and the hundreds of years of cultural interest they represent under-score Hermaphroditus as a positive symbol of appreciation for the fluidity the figure represents.

The concept of bipotentiality appears in other products of these ancient cultures, including a story by Athenian play-wright Aristophanes of the first humans, bipotential people in their entirety with all of the parts of men and women but sharing a single, spherical body. After being cleaved in two by Zeus, the split parts would spend their lives seeking one another to reunite. Taking this example as a way to represent the fluidity and change in DSDs as a fulfillment of human need rather than a derailment is one way to empower DSD individuals and their families in anticipating potential changes.

Hermaphroditus appears in the writings of Greek philosophers and historians, as well. Even the Roman orator Cicero wrote of Hermaphroditus as a second Cupid, and Hermaphroditus often was associated with eroticism and fertility. Ovid brings full characterization to Hermaphroditus in his *Metamorphosis*, detailing an allegory of puberty that ends with Hermaphroditus, having grown up as a boy, blending his body with that of an amorous water nymph to become a “creature of both sexes.”

Later philosophers of antiquity and even some Christian writers cited androgyny like this as representing human-kind’s original state of perfection, and some even viewed Hermaphroditus as representing the perfect union of marriage. Going even deeper into history, the Greeks may well have encountered this sociocultural acceptance and empowerment of the hermaphrodite nature from Eastern religions sometime around 5 BC.

Daphne: A model of positivity

Daphne represents a positive approach to metamorphosis (Fig. 3). Her story begins with Apollo angering Eros, the god of love. In revenge, Eros shoots Apollo with a golden arrow, inflaming his love for Daphne, whom Eros shoots with a lead arrow, leading her to detest Apollo. Daphne, a naiad, is committed to an active forest life as a virgin, but when Apollo begins to pursue her, she appeals to a river god to help her. The river god rescues Daphne by transforming—metamorphosing—her into a graceful laurel tree with her “shining beauty” still remaining, evergreen. Her change or transformation is viewed as a powerful and positive act instead of negative or strange and has long since been celebrated. She is no longer what she was, but she is still accepted and admired in her new form, too. Indeed, the beauty of the laurel has been revered ever since in Greek culture, from serving as the symbol of Apollo himself to forming the wreaths used to adorn victors in ancient games, including the Olympics. This symbol remains in use today as a positive representation across many cultures, including at graduations, for winners of athletic events, and in art. Everywhere one looks, one can see examples of this “shining beauty” of the metamorphosed Daphne, who in an allegory of puberty, experiences the tensions of chastity and desire and undergoes metamorphosis into an entity of lasting beauty.

Biological fluidity

The expression of fluidity exists in two ways in individuals with DSDs: biological and psychosocial. Below, we address biological fluidity as it relates to the three conditions under consideration.

Fluidity and metamorphosis with AIS

For AIS, the partial form is more likely than the complete or mild forms to display biological fluidity, particularly if a female gender is assigned at birth. In these patients, there is a possibility of virilization during puberty due to excess androgen production partially overcoming the androgen receptor resistance. However, self-initiated gender reassignment, both from male to female and female to male, is uncommon.⁹ Over the past 25 years, there has been an increasing trend in male sex assignment for patients with PAIS, likely due to increased emphasis on karyotype, improved surgical techniques, and studies showing good long-term outcomes with male sex assignment.¹⁰

Fluidity and metamorphosis with 5ARD

The same concept applies to children with 5ARD. Increased testosterone production at puberty in children with androgen insensitivity will cause more virilization. Biological fluidity is seen in this condition when patients are phenotypically female at birth and undergo virilization during puberty, though to a lesser extent than unaffected male siblings. Though the process of transformation follows normal stages of puberty, the change can come on so quickly that it may seem as though children with 5ARD go to bed with anatomically female genitalia and wake up masculinized. The mechanism is not completely understood but is thought to be due either to high levels of testosterone binding to androgen receptor or peripheral conversion of testosterone to dihydrotestosterone by peripheral 5- α reductase type 1.¹¹ At the psychosocial level, fluidity also is seen in gender, the social construction of sex. When sex is fluid, gender identity can be fluid; in one study, approximately 60% of patients are noted to have a gender role change from female to male.¹²

Fluidity and metamorphosis with gonadal dysgenesis

The potential for biological fluidity in this subset of patients exists primarily for XY individuals with PGD who have a predominately female phenotype and are not identified in the newborn period. When these patients go through puberty, virilization can occur if the dysgenetic testes can produce sufficient amounts of testosterone. A case report by Cools et al.¹³ described two 46,XY adolescents with partial gonadal dysgenesis secondary to an *NR5A1* mutation who had predominately female phenotypes at birth and subsequently developed progressive virilization in adolescence. This report highlights the fact that inadequate virilization at birth does not exclude the potential for adequate male pubertal development.

Psychosocial and ethical considerations of fluidity and metamorphosis

Models of how to approach sex assignment in DSDs have evolved. As an example, Engel's biopsychosocial model moves clinical judgment and decision-making, and therefore the counseling of parents, beyond a narrow biological view and allows for the incorporation of psychological and social factors into our understanding of disease.¹⁴ In the setting of gender fluidity, exemplified by Hermaphroditus and Daphne, this model challenges us to examine how psychological and social dimensions of sex and gender are.

For infants born with ambiguous genitalia, parents and caretakers are under enormous societal pressure to assign a sex, which has implications for gender.¹⁵ Although a comprehensive approach, as outlined below, can decrease the likelihood of gender dysphoria later in life, some patients still report dissatisfaction with the initial sex and gender assignment.¹⁶ This is most true in conditions such as partial androgen insensitivity, androgen biosynthetic defects, or incomplete gonadal dysgenesis.¹⁶

For these reasons, it becomes critical to support parents to resist undue pressures to prematurely assign a gender before a comprehensive evaluation is complete and to prepare the family for the possibility of fluidity in the form of reassignment in the future. This approach may diminish adverse psychosocial outcomes. A lack of empirical data contributes to the stress surrounding the management of intersex conditions and may exacerbate the negative long-term psychological and biological outcomes.^{17,18} Trying to assign gender based on the desire for the child to seek more socially accepted heteronormative relationships as an adult risks urologic, sexual, and reproductive dysfunction.^{15,19} Social stressors, such as the current debates over bathroom use by transgender individuals or over homosexual relationships and marriage, may lead to increased biological and psychological morbidity for these patients.²⁰

Hiding the intersex condition from children to protect them is fraught with peril. Deception may rob them of the opportunity to come to terms with their condition, leaving them vulnerable to crises of sexual identity and peer group identity.¹⁵ When possible, waiting to make a definitive gender assignment until the patient is able to participate in making the decision will potentially lessen the psychosocial consequences from confusion over gender identity.¹⁶

Sex assignment in the context of fluidity

To ensure appropriate practices and responsible management of the fluidity potential with DSD conditions, it is important to educate parents and patients about concepts of sex and gender as biopsychosocial and fluid. For standardization of this approach, clinicians need an appropriate algorithm that incorporates the concept of fluidity, and our suggested approach is given in Fig. 4.

The patient with AIS

As with other DSDs that present with ambiguous genitalia, multiple factors are involved in sex assignment in patients with AIS, including patient issues, parental concerns, medical and

surgical treatments needed, and ethical and social considerations.²¹ For AIS, there are different levels of complexity in the decision-making process for PAIS compared to CAIS.

For CAIS, patients are phenotypically female and should be given female sex assignment if diagnosed at birth. Patients are often not diagnosed until puberty, however, and have been raised as females. Although there are rare case reports of male gender identity and gender reassignment later in life, patients in general maintain female gender identity.²²

In patients with PAIS, due to phenotypic heterogeneity, a multidisciplinary approach is recommended for sex assignment. As the phenotype may overlap with other causes of ambiguous genitalia, a definitive diagnosis is recommended prior to assignment, although this may not always be possible; androgen receptor mutation screening results may be negative even in the presence of a variant because not all mutations have been characterized, and an as-yet unidentified mutation may be present.²³ External phenotype is often a major component in the decision-making process, and it has been proposed that an external virilization score may be a useful predictor.²⁴ However, external phenotype should not be the only element considered in sex assignment, because it is not the only relevant biologic consideration. Recent consensus recommendations state that for PAIS, male assignment should be based on response to testosterone therapy and genetic assessment, and female assignment should be considered in those without response to androgens.²⁵ In addition, patient or parental preference, social influences, and complexity and reversibility of surgical and medical interventions should be considered.²¹

Although gender reassignment at a later age is not common, it is recommended that nonessential and irreversible interventions, including gonadectomy and feminizing surgeries, should be deferred until patients can be involved in the decision-making process.²⁶ However, due to the risk of virilization at puberty, some have suggested that patients with PAIS who are given a female gender assignment undergo gonadectomy prior to puberty to minimize this risk.²

The patient with 5ARD

The 2006 International Consensus Conference on Intersex recommended that patients with 5ARD and ambiguous genitalia be given a male sex assignment because over 60% later identify as male, indicating significant fluidity in gender later.²⁷ However, each case still must be considered individually, based on phenotype, response to hormonal therapy, and evidence of androgen exposure particularly to the brain, because androgen exposure during fetal life may have an impact on “brain sex” and later gender identity.^{28,29} Social and cultural influences must also be considered. In addition, even though most patients eventually identify as male, there are reports describing satisfaction with female sex assignment.¹²

Currently, there is no consensus regarding surgery for 5ARD and other DSD, including indication, timing, and outcomes.²⁵ Given the fluidity of the condition and possible metamorphosis in adolescence and early adulthood, it is important that long-term follow-up is established and that extensive medical and psychosocial evaluations are performed prior to decisions regarding gender assignment and irreversible surgery. It has been recommended

that irreversible procedures be delayed until the patient can comprehend the condition and be involved in the decision-making process.²⁸

The patient with gonadal dysgenesis

In complete gonadal agenesis, a female sex assignment is given based on the fact that these patients do not have any functional testicular tissue and have completely female external genitalia. These patients typically have a female gender identity. Patients with PGD, on the other hand, must be evaluated case by case by an experienced multidisciplinary team when deciding sex assignment.

Long-term outcome studies on sex assignment in PGD patients are lacking. Many factors must be taken into account including appearance of the external genitalia, reproductive capability, sexual function, complexity of surgical and medical management, and parental preferences.³⁰ For patients with PGD who are significantly undervirilized and are given a female sex assignment, prophylactic gonadectomy is often performed because of the risk of malignancy in the retained gonads; thus, the natural course of these patients is largely unknown.³¹ In patients with ambiguous genitalia and palpable testes with evidence of significant testicular function, the general recommendation is to assign these patients a male sex. For those who are assigned male sex and have retained gonads, close monitoring is necessary given the risk of gonadal malignancy.³²

An approach that involves delaying any surgery for cosmetic reasons until the child is old enough to participate in the decision is recommended. This guidance is based on case reports of patients who were assigned a female sex at birth but who developed a male gender identity and underwent gender reassignment later in life.^{33,34} Continued long-term psychological assessment and education of these patients is necessary to evaluate for and anticipate the potential for a change in sex assignment.

The message for parents and patients

Parents need to be ready for the possibility that their children may undergo change and that such fluidity is not abnormal biopsychosocially. This puts parents on a steep learning curve. Without any groundwork or readiness, these changes can be deeply concerning to both parents and patients (Fig. 3). All involved parties must be reassured that even if changes arise during later developmental phases, these metamorphoses should be viewed as positive manifestations (the Daphne model of celebration and acceptance of transformation and change) that should not carry any social weight of shame. The Greek model is to glorify such changes rather than treating them as peculiar or strange. Patients and parents with this positive information and empowered with knowledge that the metamorphosis may happen can have an understanding of the fluidities involved that should alleviate many of the psychosocial tensions (the Hermaphroditus model of accepting multiple human forms). After all, these features have been considered culturally important and even revered at least since the time of the ancient Greeks.

Conclusions

Metamorphosis is a biological phenomenon that is intrinsic to disorders of sexual differentiation. To place the resulting fluidity of sex and gender in a positive and empowering context for patients and parents, we can look at history and understand that these entities were respected and revered in ancient Greco-Roman cultures, where they formed an expected part of the social fabric. Fluidity needs to be understood today as encompassing both biological and psychological elements, with the latter still constrained by sociocultural factors. Looking to the historical models, we want to use their lessons to empower our patients and show them that transformations were embedded in and celebrated by ancient Greek society. The models offer a biological and cultural basis for acceptance and appreciation from self and others in terms of the power of transformation (Daphne) and the acceptance and importance of multiple human forms (Hermaphroditus). The overall aim is to apply approaches that empower patients and parents using these models that predict and demonstrate respect for the fluidity of the biological aspects that may lead to metamorphosis in later developmental stages, while providing psychosocial support to families and patients in order to identify fluidity and gender nonconformity as necessary, and assist patients in identity development and expression.

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Fig. 1.

The typical differentiation pathway from the bipotential gonad to the typical male and female anatomy, with some of the involved genes. (Modified with permission from Elsevier, from Acherman JC, Hughes IA. Pediatric disorders of sex development. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology. 13th ed. Philadelphia, PA: Elsevier, Inc.; 2016: 893–963.).

Fig. 2.
Hermaphroditus. A Hellenistic statue of Hermaphroditus (marble copy of a fresco from Herculaneum). Source: Wikimedia Commons.

Fig. 3. Daphne, Apollo, and Daphne, terracotta sculpture by Massimiliano Soldani, c. 1700, Cleveland Museum of Art. Source: Wikimedia Commons.

Fig. 4.

Algorithm for responsible management: a fluidity model for providing sex assignment education based on different components of sexual differentiation—medical, surgical, and ethical considerations must be considered and balanced against patient and parent understanding and sociocultural expectations. The Greek models may serve as context for this last factor. (Adapted with permission from Pediatric Endocrinology Reviews, from Chen MJ, Vu BM, Axelrad M, et al. Androgen Insensitivity Syndrome: Management Considerations from Infancy to Adulthood. *Pediatric endocrinology reviews: PER*. Jun 2015;12(4):373–387).