Guidelines for Evaluating and Managing Children Born with Disorders of Sexual Development

Ganka Douglas, PhD; Marni E. Axelrad, PhD; Mary L. Brandt, MD; Elizabeth Crabtree, MPH; Jennifer E. Dietrich, MD, MSc; Shannon French, MD; Sheila Gunn, MD; Lefkothea Karaviti, MD, PhD; Monica E. Lopez, MD; Charles G. Macias, MD, MPH; Laurence B. McCullough, PhD; Deepa Suresh, MD; Elise Austin, MS; and V. Reid Sutton, MD

Abstract

Children born with disorders of sexual differentiation (DSD) pose numerous challenges for the parents, family, and treating physicians. The pediatrician is usually the first medical contact for newborns with DSD or for toddlers and children who present with DSD at a later time.

Several years ago, we formed a Gender Medicine Team (GMT) at Baylor College of Medicine and Texas Children’s Hospital (TCH) to explore and evaluate the most appropriate management strategies, which had long been a matter of concern and contention. Subsequently, the GMT, composed of experts in the fields of endocrinology, ethics, genetics, gynecology, psychology, pediatric surgery, and urology, formed a Task Force to evaluate the information available from our own experiences and from reviews of the literature. Utilizing the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system to assess the evidence and recommendations, the Task Force developed a consensus statement for clinical management of DSD and for making appropriate sex assignments.

1. Determine the appropriate workup and management for children aged 0 to 24 months with ambiguous genitalia or a DSD.
2. Determine sound and appropriate methods approaching sex assignment in an infant with ambiguous genitalia or a DSD.
3. Educate and refer for the appropriate surgical management of children aged 0 to 24 months with ambiguous genitalia or a DSD.

All authors are with Baylor College of Medicine Texas Children’s Hospital, Houston, TX. Ganka Douglas, PhD, is a Postdoctoral Fellow; Marni E. Axelrad, PhD, is Associate Professor, Division of Psychology; Mary L. Brandt, MD, is Professor; Elizabeth Crabtree, MPH is Research Specialist, Evidence-Based Outcomes Center; Jennifer E. Dietrich, MD, MSc, is Assistant Professor and Chief of Pediatric and Adolescent Gynecology, Division of Pediatric and Adolescent Gynecology, Department of Obstetrics, and Gynecology; Shannon French, MD, is Assistant Professor; Sheila Gunn, MD, is Assistant Professor; Lefkothea Karaviti, MD, PhD, is Professor and Director of the Center of Gender Medicine; Monica E. Lopez, MD, is Assistant Professor; Division of Pediatric Surgery; Charles G. Macias, MD, MPH, is Associate Professor and Director of The Center for Clinical Effectiveness; Laurence B. McCullough, PhD, is Professor, Center for Medical Ethics and Health Policy; Deepa Suresh, MD, is Assistant Professor, Division of Pediatric Endocrinology; Elise Austin, MS, is Genetic Counselor; and V. Reid Sutton, MD, is Associate Professor and Medical Director of Biochemical Genetics Laboratory, Department of Molecular and Human Genetics.

Address correspondence to: Lefkothea Karaviti, MD, PhD, Department of Pediatrics, Texas Children’s Hospital, Baylor College of Medicine, 6621 Fannin, Houston, TX 77030; email: lpkaravi@texaschildrenshospital.org.

The authors would like to thank Mark Kline, MD, Chairman of the Department of Pediatrics at BCM and Physician-in-Chief at TCH, for his visionary support of the Gender Medicine Clinic; Maria New, MD, for her involvement in opening the area of sexual differentiation disorders; Lee Ligon, PhD, for her unique editorial contributions and key input to the manuscript; patients in the Gender Medicine Clinic, who have been our teachers and made invaluable contributions to the development of the guidelines. The authors also acknowledge the editorial assistance of Lynda Jacks, RN.

The authors have disclosed no relevant financial relationships.

doi: 10.3928/00904481-20120307-09
Guidelines for Evaluating and Managing Children Born with Disorders of Sexual Development

Ganka Douglas, PhD; Marni E. Axelrad, PhD; Mary L. Brandt, MD; Elizabeth Crabtree, MPH; Jennifer E. Dietrich, MD, MSc; Shannon French, MD; Sheila Gunn, MD; Lefkothea Karaviti, MD, PhD; Monica E. Lopez, MD; Charles G. Macias, MD, MPH; Laurence B. McCullough, PhD; Deepa Suresh, MD; Elise Austin, MS; and V. Reid Sutton, MD

The treatment of children born with disorders of sexual differentiation (DSD) pose numerous challenges for the parents, family, and treating physicians. The pediatrician is usually the first medical contact for newborns with DSD or for toddlers and children who present with DSD at a later time.

Although the management of DSD is a developing field, the objective always is to determine the best outcome decision at the time of presentation. In general, unmanaged variations in practice lead to wide variations in outcomes, thus impeding...
the delivery of high-quality patient care. Hence, evidence-based guidelines, systematically developed recommendations that can assist the practitioner in providing diagnostic accuracy and therapeutic reliability, are needed. This paper is a continuation from the Consensus statement developed at Texas Children’s Hospital for the management of DSD. Several years ago, we formed a Gender Medicine Team (GMT) at Baylor College of Medicine and Texas Children’s Hospital (TCH) to explore and evaluate the most appropriate management strategies, which had long been a matter of concern and contention.

Subsequently, the GMT, composed of experts in the fields of endocrinology, ethics, genetics, gynecology, psychology, pediatric surgery, and urology, formed a Task Force to evaluate the information available from our own experience and from reviews of the literature. Four clinically relevant questions were identified as those that needed to be answered. Utilizing the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system to assess the evidence and recommendations, the Task Force developed a consensus statement for clinical management of DSD and for making sex assignments.

We sought to address the most common scenarios faced by the pediatrician, which usually involve answering the following initial questions:

- What is the appropriate workup for children aged 0 to 24 months with ambiguous genitalia or a DSD?
- What is the appropriate acute management for children aged 0 to 24 months with ambiguous genitalia or a DSD?
- What is the most appropriate way to approach sex assignment in an infant with ambiguous genitalia or a DSD?
- What is the appropriate surgical management for children aged 0 to 24 months with ambiguous genitalia or a DSD?

We herein summarize our approach pertaining to the general pediatrician who is confronted with the challenge of counseling the patient and family at the time of diagnosis of a DSD. Our GMT Task Force recommends:

- A laboratory workup to determine the items outlined below;
- Immediate management for acute conditions;
- Sex assignment based on an ethical framework that includes educating and involving the parents; and
- Surgical management.

APPROPRIATE WORKUP AND EVALUATION OF AMBIGUOUS GENITALIA

Evaluation will involve elucidating both sexual determination, processes that occur between conception and gonadal differentiation, and sexual differentiation, processes that occur between gonadal sex determination and maturity. Universal newborn screening for severe 21-hydroxylase deficiency has been recommended. The work of other authors and our team confirm that a multidisciplinary team is needed to counsel the family at the time of diagnosis.

The diagnostic workup should include family history, general examination for dysmorphic features, and grading based on the presence or absence of gonads and their palpability (see Table): (a) no gonads palpable (46, XX DSD, congenital adrenal hyperplasia [21-hydroxylase deficiency] or 46, XY DSD); (b) one gonad palpable, or abnormal gonadal differentiation (46, XY DSD, mixed gonadal dysgenesis [45 X/46 XY], ovotesticular DSD); and (c)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAH</td>
<td>Standard workup (electrolytes, glucose, 17OHP, plasma renin activity, D4 androstenedione, testosterone, 11 deoxycortisol, DHEA).</td>
</tr>
<tr>
<td>Hypopituitarism/hypogonadotropic hypogonadism</td>
<td>Standard workup: testosterone, LH, FSH, glucose, T4 (free thyroxine by equilibrium dialysis); TSH, testosterone, LH, FSH, random cortisol versus 1 mcg ACTH stimulation test.</td>
</tr>
<tr>
<td>Micropenis, undescended testes in the context of primary hypogonadism or in the context of evaluation of the action or production of testosterone</td>
<td>Testosterone and dihydrotestosterone at baseline followed by stimulation with hCG (500 units intramuscularly every day x 3 days for younger than 1 year of age), and draw testosterone, dihydrotestosterone on day 4.</td>
</tr>
<tr>
<td>Ambiguous genitalia</td>
<td>Genetic testing as appropriate, depending on karyotype and phenotype, including molecular genetics as needed for 5 alpha-reductase and androgen receptor defects.</td>
</tr>
</tbody>
</table>

two gonads palpable, or 46, XY DSD, impaired testosterone biosynthesis (androgen receptor defect 5-alpha-reductase deficiency, ovotesticular DSD).

Approximately 75% of patients who present in the emergency room with ambiguous genitalia with hyponatremia and hyperkalemia and a lack of palpable testes will have a diagnosis consistent with congenital adrenal hyperplasia (CAH).13 An example of classification based on palpability of the gonads is provided in Table 1 (see page e3).

But this approach is relevant to more than simply diagnosing CAH. Because of the range of disorders, it is important that pediatricians also use the common distinctions established by Prader14 to identify phenotypes of ambiguous genitalia (see Table 2).

In cases of a hypothalamic-pituitary-gonadal axis issue in the context of ambiguous genitalia or hypothalamic-pituitary hypogonadism, the underlying problem most likely is a hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator defect with subsequent hypogonadotropic hypogonadism that might be in isolation or in the context of hypopituitarism. To establish the diagnosis of isolated hypogonadism in the context of micropenis, hypopituitarism needs to be ruled out.

In typical hormone functioning, the GnRH pulse generator has developed and is functional by the end of the first trimester. Levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and sex steroid secretion are low in childhood, and male infant levels of testosterone increase during the second week, reaching a maximum at 4 to 10 weeks of life and declining to low levels by the time the child is approximately 6 months old. In cases of micropenis with or without cryptorchidism, it is imperative to exploit the window of opportunity of the LH and FSH levels to establish the diagnosis of hypogonadotropic hypogonadism. If the infantile GnRH gonadotropin spurt is captured, hypogonadotropic hypogonadism would be identified by the blunt response or ruled out by the appropriate peak, thereby precluding the uncertainties and delays in distinguishing constitutional delay in puberty from hypogonadotropic hypogonadism.

Accordingly, hormone replacement therapy can be initiated at the normal age of pubertal onset. Infants with micropenis should be administered testosterone.15 We recommend establishing the presence of hypogonadotropic hypogonadism within the first 6 months of life and initiating the appropriate hormonal replacement therapy immediately.

For the evaluation of micropenis and undescended testes in cases of primary hypogonadism most likely in the context of dyseogenic testes, we recommend using human chorionic gonadotropin (hCG) stimulation for the evaluation of primary hypogonadism and obtaining measurements of basal Müllerian inhibiting substance (MIS). The hCG stimulation test has shown a positive predictive value of 89% and a negative predictive value of 100%.16

Peripheral defects leading to micropenis might be associated with molecular genetic mutations in the androgen receptor (AR). Alternatively, micropenis and hypospadias might be a consequence of a defect in the conversion of testosterone to dihydrotestosterone in the context of 5 alpha-reductase deficiency. Evaluation then should include studying the AR expression and screening for 5 alpha-reductase mutations and evaluating testosterone levels.17,18

With regard to the production of testosterone involving enzymatic machinery, administering hCG to patients to increase androstenedione secretion allows for establishing the diagnosis in prepubertal individuals; in cases of suspected complete or partial androgen insensitivity, AR gene molecular testing allows for detection of hundreds of clinically recognized mutations and provides further confirmation of the clinical diagnosis. Performing molecular genetic testing on the SRD5A2 gene for 5 alpha-reductase deficiency confirms affected status suspected biochemically.

Genetic testing for ambiguous genitalia includes karyotype analysis on peripheral blood or skin fibroblasts derived from genital skin or other sources; fluorescence in situ hybridization (FISH), which provides rapid analysis and evaluation for sex chromosome

### TABLE 2: Prader Staging

<table>
<thead>
<tr>
<th>Prader Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Slightly virilized female, perhaps only exhibiting isolated clitoral hypertrophy and without labial fusion.</td>
</tr>
<tr>
<td>II</td>
<td>Clitoromegaly and posterior labial fusion: narrow vestibule at the end of which the vagina and the uretha open.</td>
</tr>
<tr>
<td>III</td>
<td>Greater degree of clitoromegaly, single perineal urogenital orifice, and almost complete labial fusion.</td>
</tr>
<tr>
<td>IV</td>
<td>Phenotypic male with hypospadias and microgenitalia: increasingly phallic clitoris, urethra-like urogenital sinus at base of clitoris, and complete labial fusion.</td>
</tr>
<tr>
<td>V</td>
<td>Cryptorchid boy: penile clitoris, urethral meatus at tip of phallus, scrotum-like labia and non-palpable gonads.</td>
</tr>
</tbody>
</table>

mosaicism and/or chimerism; FISH for determining the presence or absence of the sex-determining region on the Y chromosome (SRY); specialized molecular genetic testing for Y-chromosome deletions; and the array comparative genomic hybridization (aCGH).19

The aCGH is proving useful in evaluating cases of ambiguous genitalia by simultaneously providing the same information as a standard karyotype, evaluating for sex chromosome mosaicism and/or chimerism, and detecting the presence or absence of SRY and other copy number changes that may cause DSD.20

Hence, the GMT Task Force recommends a multidisciplinary approach using various diagnostic procedures, including karyotype, and additional appropriate testing such as aCGH for the genetic workup of infants with ambiguous genitalia or a DSD. The work of other authors and our team confirm that a multidisciplinary team is needed to counsel the family at the time of diagnosis.22 Laboratory workups to identify phenotypes of ambiguous genitalia are listed in Table 1 (see page e3).

**ACUTE MANAGEMENT OF INFANTS WITH AMBIGUOUS GENITALIA/DSD**

For infants with ambiguous genitalia or a DSD who present with a life-threatening complication like the ones described below, we recommend initiating treatment with stress-dose steroids immediately while waiting for laboratory test results.

We concur with other authors11,14 that the emergency conditions should be addressed as follows: (a) for cases of suspected CAH (salt-losing variety), a laboratory workup should be initiated, and the infant should be treated with D5 NS (dextrose in normal saline) and stress steroids (hydrocortisone 100 mg/m²/day), with treatment modified after 24 hours, based on electrolyte correction.

Mineralocorticoids (fludrocortisone, 0.1 mg by mouth once each day should be added, with a switch to table salt (1 to 2 g by mouth once each day,21 given in 24-hour worth of formula or breastmilk); (b) for cases of microcephaly and suspicion of hypopituitarism (the concern is hypoglycemia), the pituitary adrenal axis should be assessed for production of cortisol and treat-

In addition to medical personnel, our team approach also includes a psychologist and an ethicist.

ment (stress steroids: 100 mg/m²/day hydrocortisone) should be initiated while laboratory results are pending; and (c) for cases of suspected CAH in crisis, hydrocortisone stress doses should be initiated IM or IV. For long-term management of CAH, we recommend as per the literature glucocorticoids (hydrocortisone 10 to 20 mg/m²/day, divided by three doses per day, mineralocorticoids (fludrocortisone, 0.1 to 0.2 mg daily) and sodium chloride (1 to 2 g or 17 to 34 mmol of sodium chloride daily).21 Since aldosterone regulates sodium homeostasis, IV normal saline administered during adrenal crisis along with emergency glucocorticoids corrects the hypovolemia and hyponatremia.

**SEX ASSIGNMENT IN AN INFANT WITH AMBIGUOUS GENITALIA/DSD**

Making sex assignments for infants born with ambiguous genitalia or DSD involves numerous considerations. Our guidelines not only address medical considerations, but also ethical and legal matters as well.

With regard to whether sex assignment should be physician-dependent or reside within a GMT, we base our guidelines on systematic reviews of the literature,22 as well as our own accumulative experience at TCH,1,12 and recommend using a consensus approach that includes an ethical framework for informed parental decision-making.

Our multidisciplinary GMT approach used at TCH is designed to meet the multifaceted needs of individuals with DSD and is recommended over the traditional physician-determined approach.1 In addition to medical personnel, our team approach also includes a psychologist and an ethicist.1,12 It also includes: an ethical framework involving a team of specialists; and education and participation of the parents in the decision-making process.

Although specific guidelines have not been established heretofore, our experience and the few outcome studies,18,23,24 have shown that parents and other family members experience uncertainty about the future and how to explain situations to others; they occasionally demonstrate significant symptoms of anxiety and depression during diagnosis, medical workup, acute management, sex assignment, and treatments.

Patients themselves often experience various psychosocial challenges that may require psychological intervention. For these reasons, we recommend including a psychologist on the multidisciplinary team to provide immediate and ongoing support to both patients and caregivers.1,12

Our GMT was the first multidisciplinary team to include an ethicist. We base this inclusion on: 1) the identified need to determine ethical judgments on an evidence-based assessment of the affected infant; 2) the centrality of making decisions in the best interest of the infant and the child and adult that infant will become; 3) the obligation of health care professionals to include the
parents in the decision-making process that will also involve providing them with education; 4) the need to include the child in the decisions that will be made appropriate to the developmental stages; and 5) the obligation to consider the biopsychosocial variations in sex, gender, and gender identity, as well as cultural changes that are likely to result.

Responsible management of DSD is guided by two ethical considerations: 1) the variations in the different components of biological sex, including genomic sex, anatomic sex (internal and external), hormonal sex, and brain sex, and the variations that will be observed in subsequent gender, including gender identity and sexual orientation; and 2) the prevention of irreversible anatomic and physiologic effects of surgical assignment, particularly when the components of biological sex do not strongly align.

Descriptions of ethical frameworks and a statement from an interdisciplinary research group\(^{25,26}\) confirm our inclusion of an ethicist. We strongly recommend consulting an ethicist familiar with ethical issues in DSD on each case to ensure that the patient’s individual needs are addressed in accordance with the ethical framework established by the GMT.

**APPROPRIATE SURGICAL MANAGEMENT**

When to perform surgery and the appropriate surgical management of the infant with ambiguous genitalia or DSD have been matters of contention for some time, especially since the initial studies by Money\(^{27}\) were challenged. Each case is different, but certain guidelines have been established by our GMT.

**Surgical Management for Infants with CAH**

For genetically female infants born with CAH with virilized external genitalia, most studies and our experience indicate that patients benefit from early one-stage reconstructive surgery,\(^{11}\) with the patient’s steroid replacement increased beforehand. The mainstays of surgical repair are clitoral resection, correction of the urogenital sinus defect that results from failure of the vagina to complete the migration to the perineum, and exteriorization of the vagina, which may require that the labioscrotal folds be trimmed, thinned, and elongated to create labia majora with a more normal appearance.

**Feminizing Surgery for Patients with DSD**

Surgical management of infants born with DSD is complex and must be designed individually with the following goals in mind: preserving normal genital sensation, creating a normal introitus, and providing an adequate vaginal opening at the perineum.

Consensus statements addressing DSD show a clear trend toward multidisciplinary management, with pediatric surgeons, urologists, and gynecologists advocating individualized approaches. Most consensus statements recommend early surgical correction once the evaluation is completed, although some organizations delay surgery until the patient reaches an appropriate age of informed consent.

Our team recommends that cases be individualized due to the spectrum of presentation, and that surgery be delayed until a definitive gender assignment can be established.

**Masculinizing Surgery for Patients with DSD**

For patients with 46,XY DSD, the surgical approach also is complex, with opinions varying on the appropriate technique and timing of surgical intervention. The surgical techniques used in masculinizing genitoplasty reconstruction include staged vs primary hypospadias repair with chordee release, scrotoplasty, orchiopexy, open or laparoscopic removal of Müllerian structures, and insertion of testicular prostheses.

As with feminizing surgery, the results have varied considerably. We recommend: postponing surgical management until concordance is established and medical therapy is given; performing masculinizing genitoplasty and orchiopexy for under-androgenized male patients with underlying testosterone deficiency, especially 17-beta hydroxysteroid dehydrogenase deficiency; and providing preoperative testosterone stimulation followed by hypospadias repair and scrotoplasty, as well as dihydrotestosterone replacement, for under-androgenized male patients with 5-alpha-reductase deficiency.

**Gonadectomy Surgery for Patients with DSD**

Several reports describe the association of 46,XY gonadal dysgenesis with gonadoblastoma and risk of malignancy. Predominant risk groups include syndromes of gonadal dysgenesis and Ullrich-Turner syndrome. Certain syndromes with splice variants of the \(WT1\) gene are susceptible to Wilms’ tumors.

In cases of gonadal dysgenesis, we recommend performing early gonadectomy; however, in cases of complete androgen insensitivity syndrome (CAIS), we recommend delaying surgery until after the patient reaches puberty.

**CONCLUSIONS**

Following evidence-based guidelines is essential in practice to provide patient-centered, effective, and efficient management of patients with DSD. Once a DSD has been identified, the pediatrician needs to rule out a medical emergency in the context of hypopituitarism or CAH. The appropriate workup needs to be initiated according to the phenotype and clinical assessment.

Based on our experience in this field and our reviews of approaches taken by other experts, we recommend after these steps have been taken that the general
pediatrician refer the patient to a center with a multidisciplinary team that includes an ethicist who can ensure that the sex-assignment decision is made within an ethical framework for treating persons with DSD. We also recommend involving the parents as active participants after providing them adequate education regarding their child’s condition, the various options available, and the likely best outcomes based on the information available. We target our management for gender stability by providing support through a psychologist in the event of a sex change, should that be the choice of the individual.

REFERENCES


