The Newborn with Genital Ambiguity

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Conflict of Interest Statement

• I have no conflicts of interest or relevant financial relationships with any commercial entities.
• I will not be discussing off-label use of any medications or devices.
• I am a member of Medical Advisory Board for the AISDSD family support group.

Lecture Outline

• Learning objectives
• Review embryology of sex development
• Etiologic classification
• Approach to work-up
• Current standards of care
• Evolving Best Practices
• Recent Legal and Ethical developments

Learning Objectives

• Be familiar with currently accepted nomenclature.
• Review embryology of normal sex development.
• Understand which disorders are common.
• Appreciate importance of prompt, family-centered, team approach to work-up.
• Be familiar with some appropriate steps in initial work-up or a newborn with atypical genitalia.
• Be familiar with evolving trends in ethics, informed consent, human rights issues in the field.
Embryology of Sex Development

Gonadal Differentiation

- Expression of “master gene” SRY at 6 weeks gestation
- Other genes known to be involved as of 2015:
  - SF-1/NR5A1
  - WT-1
  - DMRT1
  - DAX1/NROB1
  - SOX-9
  - Wnt-4

External Genital Differentiation

9-14 weeks gestation

Etiologic Classification of Disorders (Differences; Variation) of Sex Development

See also: aboutkidshealth.ca/En/HowTheBodyWorks/SexDevelopmentAnOverview
**Disorder of Sex Development (DSD)**

- Nomenclature developed at 2005 Consensus Conference in Chicago
- Marked improvement in terminology
- Useful for taxonomy and guiding work-up
  - 46, XX DSD
  - 46, XY DSD
  - Sex chromosome DSD

**Definition of Disorder of Sex Development (DSD)**

- Broad array of conditions in which development of the chromosomal, gonadal, or phenotypic sex is atypical.
- Encompasses:
  - Ambiguous external genitalia
  - Incomplete development of sex anatomy
  - Disorders of gonadal development
  - Disorders of hormone synthesis or resistance
  - Sex chromosome anomalies
- May not present until puberty.

**Alternate Designations**

- Difference in sex development
- Variation in sex development
  - (but “VSD” is already taken)
- Atypical sex development
- Atypical genitals
- Intersex

**Obsolete Nomenclature**

- Use of older terms such as
  - “hermaphrodite”
  - “pseudohermaphrodite”
  - “testicular feminization”
  - “sex reversal”
- Are outmoded.
  - Reported as confusing, offensive, or stigmatizing by individuals and families
  - Are no longer in use
  - Should not be part of the medical record in current era
### Nomenclature

- Affected adults and families may reject the DSD label, or may identify with different terminology,
  - “differences in sex development”
  - “genital variation”
  - “atypical genitalia”
  - “intersex”
- Groups of affected individuals such as those with Turner syndrome or CAH may reject the DSD umbrella outright.

### Common DSDs

- Klinefelter's syndrome
- Turner's syndrome
- 21-Hydroxylase deficiency
- Hypospadias

### Incidence of DSDs

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Klinefelter Syndrome</td>
<td>1:500-1:1000</td>
</tr>
<tr>
<td>&quot;Not XX and not XY&quot;</td>
<td>1:1666</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>1:2000</td>
</tr>
<tr>
<td>Mosaic Turner Syndrome (various karyotypes)</td>
<td>1:2000</td>
</tr>
<tr>
<td>Classic Turner Syndrome (45, X)</td>
<td>1:5000-10,000</td>
</tr>
<tr>
<td>Mayer-Rokitansky-Kuster-Hauser</td>
<td>1:5000</td>
</tr>
<tr>
<td>21-Hydroxylase deficiency CAH</td>
<td>1:10,000-15,000</td>
</tr>
<tr>
<td>Rarer than 1:15,000:</td>
<td></td>
</tr>
<tr>
<td>Androgen Insensitivity Syndrome (AIS)</td>
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<tr>
<td>Complete gonadal dysgenesis</td>
<td></td>
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<tr>
<td>Ovotestes</td>
<td></td>
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<tr>
<td>Hypopituitarism</td>
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<tr>
<td>Idiopathic</td>
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### 46, XX DSD

- 21-hydroxylase deficiency will represent approximately 50% of this group.
- Other diagnoses:
  - Gonadal dysgenesis
  - Ovotesticular DSD
  - Prenatal androgen excess other than 21-hydroxylase deficiency
  - Multiple congenital malformations
### 46, XY DSD
- Inborn error of androgen synthesis
- Androgen insensitivity syndrome (AIS)  
  (partial [PAIS] or complete [CAIS])
- 5-α-reductase 2 deficiency
- Inborn error of MIS/AMH synthesis or action
- Gonadal dysgenesis
- Ovotesticular DSD
- Congenital hypopituitarism
- Multiple congenital malformations

### Sex Chromosome DSD
- 45, X and variants: Turner syndrome
- 46, XX /45, X mosaicism
- 46, XX /46, XY mosaicism
- 46, XY/45, X mosaicism
- 47, XXY and variants: Klinefelter syndrome

### Multiple Congenital Anomalies
- In the presence of other somatic anomalies, it is *unlikely* that a separate DSD would be identified.
- The etiology of the non-genital anomalies is very likely the etiology for the genital anomalies as well.
- Identifiable DSD is unlikely:
  - Premature
  - LBW
  - 46, XY
- It is appropriate to share this information with the family immediately.

### Approach to Work-up of the Newborn with DSD
Role of the Pediatrician in Evaluation of DSD

- Comprehensive work-up and evaluation of an infant with a DSD does not fall within the purview of the primary care physician.

- The appropriate role for the primary care clinician or neonatologist is recognition and prompt referral of a newborn with suspected DSD to the multidisciplinary DSD team, or transfer to the nearest center of excellence with a DSD team.

- Since CAH can be life-threatening, and since DSDs are discomfiting for the parents, expeditious evaluation represents the standard of care.

Recognition of Possible DSD in Newborn

- Small penis
  - In term infant: <2.5 cm stretched length from pubic ramus, <0.9 cm mid-shaft diameter

- Clitorimegaly
  - In term infant: >1 cm stretched length from pubic ramus, >0.6 cm mid-shaft diameter

- Posterior labial fusion
  - >50% of perineum from base of clitoris to anus is fused

- Hypospadias
- Bilateral undescended testes
- Inguinal mass in a phenotypic female
- Markedly asymmetric external genitalia

Classification System - Prader

Ambiguous genitalia
Diagnostic Studies

- Karyotype
- Imaging: ultrasound, genitogram/VCUG
- Testosterone, dihydrotestosterone, MIS/AMH
- DNA/Molecular studies*  \( \text{not always available} \)
- Adrenal intermediates**  \( \text{no sooner than day 3} \)
- Gonadotropins
- Other pituitary hormones

Sample Approach to Work-Up in a Newborn with Atypical Genitalia

- Day 1:
  - Speak with parents
  - Physical exam in presence of parents, explaining what you are seeing, \textit{but not interpretation} of the findings.
  - Examine for any additional non-genital anomalies
  - \textit{Contact DSD team}
  - Karyotype – ask the lab for stat sex chromosomes
  - Consider abdominopelvic imaging:
    - ultrasound
    - contrast study analogous to VCUG ("genitogram")
    - in some centers, MRI may be recommended

Sample Approach to Work-Up

- Day 3 or 4:
  - Draw electrolytes, LH, FSH
  - Draw testosterone, dihydrotestosterone
  - Draw adrenal intermediates
  - Brain MRI if hypothalamic-pituitary hormones are low

- Day 7:
  - Consider sending AMH/MIS
  - Repeat adrenal intermediates and testosterone

Cases
<table>
<thead>
<tr>
<th>Case A:</th>
<th>What would you do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>– 37 week infant</td>
<td></td>
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<tr>
<td>– micropenis</td>
<td></td>
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<tr>
<td>– no palpable testes</td>
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<tr>
<td>– delayed transition</td>
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<td>– moderate hypotonia.</td>
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<table>
<thead>
<tr>
<th>Case B:</th>
<th>What would you do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>– term infant</td>
<td></td>
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<tr>
<td>– ambiguous external genitalia</td>
<td></td>
</tr>
<tr>
<td>– no palpable testes</td>
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</tbody>
</table>
• Case C:
  – term infant
  – ambiguous external genitalia
  – one or both testes palpable.

What would you do?

Data from Cambridge DSD Database

• Case D:
  – term infant
  – prenatal diagnosis was 46, XY, but at birth, infant has entirely typical-appearing female external genitalia
What would you do?

Current Standards of Care

- Case E:
  - 33 week SGA infant
  - small penis
  - hypertelorism
  - low-set ears
  - heart murmur
  - unusual fingers, overriding toes.
Patient/Family-Centered Approach to Care:  
“You Never Have a Second Chance to Make a Good First Impression”

• It is critical that all health care professionals involved in the child’s care behave in a calm, thoughtful, and professional (but not cold) manner. Many parents report having been unintentionally traumatized by naïve or insensitive comments.

• “The importance of the impressions formed by parents of intersexed children during the initial encounter with the medical system cannot be overemphasized. Countless families recall the exact words used by health care providers during these initial encounters, and extreme vigilance needs to be used to prevent the common pitfalls of providing too much detail or being overly reassuring about the outcome. Controversies, complaints, and dilemmas of intersex, including the controversy regarding early genital surgery, should be presented and discussed openly.”

  Houk and Lee, Endocr Metab Clin N Am 2005

Patient/Family-Centered Approach to Care

• Full but compassionate disclosure
• Use of honest, clear terminology
• Full family participation in decision making
• Fully informed consent for any surgical procedures
• Provision of peer and psychological support
• Staged, age-appropriate full disclosure to the child
• Reduction of shame

Strategies for Bedside Care

• Reinforce “your healthy baby” (when accurate)
• Be matter of fact.
• Reassure parents that:
  – Variations in genital appearance are more common than people would think.
  – There is wide variability in genital appearance even in “normal” children.
• If asked, indicate that there is no way to know in the newborn period whether any baby will grow up to be homosexual.
• Respect privacy: Do not bring in other staff who are not involved in the case to examine genitalia.

Information You Can Provide to Families at the Bedside

• Family support for their infant is much more important than what their infant looks like.
• Scripts for dealing with extended family, baby-sitters
• Encourage parents to access support groups on-line.

• Access to family support websites
  – dsdfamilies.org
  – aisdsd.org
  – caresfoundation.org
  – accordalliance.org/dsd-guidelines
**Information You Can Provide to Families at the Bedside**

- What is and is not known about treatment outcomes.
- There may be treatment approaches which do not involve surgery.
- **Do NOT offer your “best guess” to diagnosis or gender assignment, even if the parents push you to do so. Defer to team.**

**Sharing Findings with the Family**

- Explain to the parents that the best course of action may not be clear initially, but the health care team will work with the family to reach the best possible set of decisions in the circumstances.
- Although a specific molecular diagnosis is identified in only about 20% of gonadal differentiation defects, it is most appropriate that the specific name of the condition be used as soon as it is known.

**Reduce Stigma in the Medical Record**

- **Problem List example:**
  - Cyanosis
  - Congenital heart disease
  - Tetralogy of Fallot

- **Discharge Summary:**
  - Use specific diagnosis, if known
  - Use “46, XX DSD” if that is most refined diagnosis available at discharge, NOT “Ambiguous Genitalia.”

**Gender Assignment**

Gender assignment is based on:

- Etiologic diagnosis
- External genitalia and their future functional possibilities
- Internal genitalia and fertility potential
- Potential prenatal hormone action on the CNS
- Potential surgical options
- Psychological support for parents
- Psychological support for infant from parents, family and social environment
- Parental cultural, religious values, and preference
Initial Gender Assignment

- All children should receive a gender assignment within a few weeks of birth.
- Gender assignment is based, after hormonal, genetic, radiologic tests, and consultation between parents and doctors, on which gender the child is more likely to feel as he or she grows up.
- This should be considered preliminary, since in children with some specific diagnoses, for instance PAIS, up to 25% will change gender assignment in their teens, irrespective of the decision made in the newborn period.

Outcomes of Gender Assignment

- Flexibility is the key.
- Cues from the child as he/she grows:
  - Neither pink tutus nor toy guns may be preferred.
  - Child stating firmly and consistently prior to age 5 that they are the other sex, insisting on being called by a name generally associated with the other sex, and cutting hair/wearing hair in another fashion is strong evidence of gender identity.
- Atypical gender role behavior is more common in children with DSD than in the general population, but should not be taken as an indicator for immediate gender reassignment.

What to Do About the Birth Certificate?

The following countries have some form of legal recognition for a third sex, or postponing designation of sex of newborn:
- Germany
- Australia
- India
- Pakistan
- Nepal

Evolving Best Practices
Current Topics

- Interdisciplinary care teams
- Strategies to refine information on development of gender identity
- Physical appearance of variant genitals
- Family psychosocial adjustment
- Outcome studies on adults who underwent different treatments, or no treatment at all
- When is genital surgery in order?

Optimal Interdisciplinary Teams

- Require stable, extensive staff

<table>
<thead>
<tr>
<th>Genetics</th>
<th>Endocrinology</th>
<th>Urology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynecology</td>
<td>Psychology</td>
<td>Social Work</td>
</tr>
<tr>
<td>Ethics</td>
<td>Neonatology</td>
<td>Support Groups, Religious Leaders</td>
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</table>

- Generally large academic medical centers
- Team meeting before clinic (e.g. Cleft Palate Clinic)
- DSD-TRN: NIH-supported network of 14 US Centers working together to determine what works best for affected individual and their family over developmental lifespan.

Gender Identity

- Psychosocial factors do influence gender identity development.
- Gender dysphoria and gender reassignment do occur more frequently in the DSD population than in the general population.

Sex Hormones Influence:

- Toy and play preferences
- Aggression
- Empathy
- Interest in babies
- Spatial, motor, and verbal abilities
- Gender identity
- Sexual orientation
- Sexual behavior
### Gender Identity Development

- Permanent changes in brain in utero and in first months = *Organizational effects*
- Temporary changes to the brain that affect behavior only when the hormones are present (i.e. puberty) = *Activational effects*
- *Increased recognition of the role of in utero androgen exposure.*

### Current Effort:

- Defining the prenatal and early post-natal antecedents which cement gender identity
- Prenatal testosterone exposure clearly impacts:
  - 46, XX CAH
  - 46, XX Placental aromatase deficiency
  - 46, XY Cloacal exstrophy
  - 46, XY 5α-Reductase deficiency

### Atypical Appearance of Genitals

- May elicit social stigmatization
  - Undermine self-esteem
  - Avoidance of intimacy
- Genital plastic surgery intended in all good faith to alleviate this problem, comes with its own risks:
  - Esthetic appearance
  - Scarring
  - Reduced sensation
  - Reduced functionality

### Family Interpretation

- Families may assume that a medical diagnosis mandates a certain treatment pathway.
- Families may interpret a medical approach, defining the situation as a medical “problem” requiring treatment or fixing, as requiring early surgery.
- Family desire for closure, and to put this episode behind them.
Psychosocial Adjustment

• Although clinical practice may focus on gender assignment and genital appearance, stigma and “lived experiences” with DSD are more salient issue for many affected individuals.
• In contemporary US and European society, this is changing rapidly, driven by patient advocacy groups, and buoyed by the LGBT movement.

Lessons Learned from Longitudinal Care of Children with Spina Bifida and Craniofacial Defects

• Parents have dramatic internal struggles laden with:
  – Shame
  – Guilt
  – Fear
  – Sadness
  – Grieving for loss of anticipated “perfect child”
  – Sense of responsibility

Lessons Learned from Longitudinal Care of Children with Spina Bifida and Craniofacial Defects

• Support from psychologist in both directions
  – helping the family directly.
  – helping the medical team understand the family’s current thoughts and functioning.

Peer Support from Other Affected Individuals and Support Groups

• Peer support is very helpful.
  – Well-adjusted adults with the same condition
  – Parent support groups (aisdsd.org; dsdfamilies.org)
• Peer support ends isolation and stigma.

Peer Support from Other Affected Individuals and Support Groups

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Genital Surgery

- Life-saving surgical procedures are always indicated.
- “Until recently, the surgical approach to the intersexed child was to attempt to normalize the genitalia, in other words, to reconstruct the genitalia to resemble those of a typical boy or girl. However, the goal of creating a cosmetically authentic appearance as well as fully functional and sensitive genitalia may be mutually exclusive goals...” Houk and Lee, Endocr Metab Clin N Am 2005
- Surgical procedures to allay parental distress are now discouraged, and psychological support provided.

Outcomes of Genital Procedures

- It must be anticipated that any surgical reconstruction undertaken in infancy will need to be refined at the time of puberty.
- Multiple revisions are not uncommon.
- It is appropriate to provide anticipatory guidance for families that this is the case.
- Psychosexual outcomes in adults of procedures done in childhood, and those who did not undergo any surgery, are just beginning to be studied.

Shared Decision-Making

- Shared decision-making when there is no clear-cut “best choice”.
- Decision Aids and Support Tools (DASTs)

Decision Aids and Support Tools (DASTs)

- System being developed based on published Decision Aids and Support Tools that have been used in several areas of adult medicine and oncology, to assist families and health care providers in considering clinical options for newborns with DSD.
- May become available on-line for parents to work through decisions and options.
Recent Legal and Ethical Developments

Recent Developments

- German birth certificate law
- Swiss Bioethics Commission
- Australian Senate Committee Report
- WHO statement
- M.C. v. MUSC case
- J Urology paper on outcomes in severe hypospadias
- UN Special Rapporteur on Torture
- UN Committee on the Rights of the Child

Swiss National Advisory Commission on Biomedical Ethics

Nov. 2012

“An irreversible sex assignment intervention involving harmful physical and psychological consequences cannot be justified on the grounds that the family, school or social environment has difficulty in accepting the child’s natural physical characteristics ... If such interventions are performed solely with a view to integration of the child into its family and social environment, then they run counter to the child’s welfare.”

Ethics

- The right of the child to an “open future” should generally determine the course of treatment.
  - Possibility of gender reassignment
  - Retain gonads whenever possible
- Effort in the broader society for acceptance of the children as they are.
  - Precedent from the disability community
### Ethics

- “The ethical question that must be asked at the time of sex assignment is, “Will this child thank you for this decision when it (sic) is an adult?”

  *Kipnis & Williamson, 1984*

### Gonadectomy

- Physician has the duty to protect the child from unnecessary surgery requested by the parents in other medical circumstances.
- Parents generally cannot consent to elective sterilization of a minor without approval by a court.
- However, there are as yet no court decisions regarding how these laws apply to cases of DSD.
- Until the law is settled, legal and ethical consultation advised before any non-emergent removal of gonads.

### Colombian High Court Decisions (1999)

As the results of cases regarding two young children, parents may consent to genital surgery only if:

- Child is still under age 5
- The family has been given accurate information on the risks of the procedure(s)
- The family has been informed of the existence of alternate treatment paradigm(s) that do not include early surgery
- This material has been provided in written form on two separate occasions

*No genital surgery is allowed over age 5, until the youth is old enough to consent to their own surgery.*

### Full Disclosure for Informed Consent

- Time-consuming
- Likely to require repetition
- Absence of robust outcome data on which to base decision
- Additional challenges if low health literacy and/or non-English speakers
Liability

• Trend is attempt at redress and compensation if there has been insufficient informed consent for genital surgery.
• Other professionals involved in the case may be sued, not just the surgeon.
• Facility may be sued if family is not fully informed.

Thank you for your attention.

Questions?
¿Preguntas?