Objectives: Participants will be able to:
1. Apply the medical definition for intersex in care of patients
2. Use shared decision making to determine the patient needs and develop/manage treatment plan
3. Work in interdisciplinary teams to educate and counsel patient/parents to promote well-being

I nor my partner have any relevant financial interests to disclose.

Goals
- Historical perspective of intersex
- Overview of normal sexual development
- Review of DSD: representative examples
- Long Term Outcomes/ Gender Identity

Disclaimer: Gender identity/assignment in DSD patients is at times a complex and difficult task requiring ideally a multidisciplinary team of experienced providers. I will provide a pediatric endocrine perspective to DSD, without specific all encompassing recommendations, as challenging cases should be approached on a case by case basis.

Historical Context of Intersex
- Hermaphrodites
  - Frequent discussion in Greek mythology
  - Continued in ancient Roman times
    - 16 accounts from 209 to 92 B.C. written by Titus-Levy
- Greek and Roman times (prior to 1st century AD)
  - Laws requiring exposing newborn children with ambiguity seen as sign of evil, and cast beyond limits of city

History of Intersex: America
- Early American medical texts (1600s)
  - Monstrous births
- Parsons (1741) treatise on hermaphrodites
  - Impossible for “double Nature”
- 1800s: No true hermaphrodites
  - Drive to identify “true” sex, if not able, doctors to help
  - Terms of that era: “hybrid,” “imposter,” “unfortunate monstrosity”, “these mortifying and disgusting imperfections”
History of Intersex: America
- Mid-1800s
  - Concentration on sex assignment, people with behaviors atypical were viewed as suspicious and deceptive
  - Doctor exams at times would lead to reassignment, despite individuals seemingly stable in their gender identity

American Intersex History
- Mid-1900s
  - Increased knowledge regarding importance of chromosomes and hormonal production
  - External genitalia morphology still elevated in importance
  - John Money
    - "The chromosomal sex should not be the ultimate criterion, nor should the gonadal sex. By contrast, a great deal of emphasis should be placed on the morphology of the external genitals and the ease with which these organs can be surgically reconstructed to be consistent with assigned sex."

Typical Sexual Differentiation
- Genetic
  - 46 XX female, 46 XY male determined at fertilization
- Gonadal
- Ductal Differentiation
  - Müllerian ducts, Wolffian ducts
- External Genitalia
  - Recognizable male vs female by 3 months gestation

Gonadal Sex
- Gonadal ridge forms at 5 wk
  - Remains undifferentiated for 2 weeks
- Y chromosome SRY gene activates TDF
  - Testis begins with immature germ cells
  - Somatic cells → Sertoli cells → MIS
  - Mesenchymal cells → Leydig cells → testosterone
  - Absence of SRY → ovary (noted by 9-10th week)

Ductal Differentiation
- Male
  - MIS causes degeneration of Müllerian (ipsilateral)
  - Wolffian maintained by testosterone production
  - By 7th week Wolffian system in place
    - Epididymis, vas deferens, seminal vesicles, and ejaculatory ducts

Ductal Differentiation
- Female
  - Wolffian duct undeveloped in absence of testosterone
  - Müllerian duct preserved in absence of MIS
  - By 8th week, Müllerian structures in place
    - Fallopian tubes, uterus and upper third of vagina
External Genitalia

- Local androgen (DHT) leads to differentiation
- Genital tubercle
  - Corpora cavernosa of penis or clitoris
- Urethral folds
  - Fuse to form corpus spongiosum and penile urethra or remain unfused as labia minora
- Labioscrotal swellings
  - Fuse with rugation to form scrotum or labia majora

External Genitalia

- Testicular Descent
  - Transabdominal phase
  - Inguinocrotal phase
- Urethra fusion
  - Hypospadias with inadequate androgen effect
  - Urethreal migration to clitoris with excess androgen

Murphy, et al., J Ped Adol Gynecol, 2011
Biason-Lauber, Amt Prac & Res Clin Endo & Met, 2010
Ambiguous Genitalia

- Genital anomalies affect 1 in 4500 births
- Broad differential diagnosis and approaches to classification
  - Chromosomal, hormonal, metabolic, structural
- Terms no longer recommended
  - Intersex, pseudohermaphroditism, hermaphroditism, sex reversal, gender based diagnostic labels

Disorders of Sex Development (DSD)

- International meeting (LWPE/S ESPE) in 2006
- “Congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical”
- Attempt for descriptive terms reflecting genetic etiology (not sex based)

<table>
<thead>
<tr>
<th>Sex Chromosome (DSD)</th>
<th>46, XX DSD</th>
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<tbody>
<tr>
<td>46,XX Turner and variants</td>
<td>maternally inherited androgen excess</td>
</tr>
<tr>
<td>46,XY Klinefelter and variants</td>
<td>46,XY ovarian dysgenesis</td>
</tr>
<tr>
<td>46,XY/47,XXY mosaic</td>
<td>Genital abnormalities</td>
</tr>
<tr>
<td>48,XX/47,XXY mosaic</td>
<td>46,XX ovotesticular DSD</td>
</tr>
</tbody>
</table>

**46, XX DSD**

- Typically female internal genitalia, external genitalia virilized in utero from androgen exposure
  - Maternal origin of androgen excess
  - Fetal origin of androgen excess
- Rarely gonadal (ovarian) development
  - Ovotesticular DSD, Testicular DSD (SRY +), gonadal dysgenesis

**Table 1.** Disorders of sexual development (new DSD nomenclature)

<table>
<thead>
<tr>
<th>Sex Chromosome (DSD)</th>
<th>Disorders of Testicular Development</th>
<th>Disorders of Ovarian Development</th>
<th>Female Androgen Excess</th>
<th>Non-CAH</th>
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<td>46,XX Turner and variants</td>
<td>Complete Androgen Insensitivity Syndrome/Action</td>
<td>Androgen Detected</td>
<td>+31 OH Deficiency</td>
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<tr>
<td>46,XY Klinefelter and variants</td>
<td>Partial Androgen Insensitivity</td>
<td>Androgen Detected</td>
<td>+31 OH Deficiency</td>
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<td>46,XY/47,XXY mosaic</td>
<td>Gonadal Regression</td>
<td>Androgen Detected</td>
<td>+31 OH Deficiency</td>
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<tr>
<td>46,XY/47,XXY mosaic</td>
<td>Ovotesticular DSD</td>
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<tr>
<td>46,XY/47,XXY mosaic</td>
<td>Testicular DSD (31, Xp, 46,XY)</td>
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Ocal, J Clin Res Ped Endo, 2011

<table>
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<td>[Image 1]</td>
<td>[Image 2]</td>
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</table>

Murphy, et al., J Ped Adol Gynecol, 2011
Congenital Adrenal Hyperplasia (CAH)

- Adrenal cortex enzymatic deficiency preventing adequate adrenal hormones
- Most common enzyme deficiency is 21-hydroxylase making up ~90% of CAH patients, affecting ~1 in 15,000
- Female infants will be born virilized (variable degree), perhaps with salt loss as well

CAH due to 21-Hydroxylase deficiency

- Medical Treatment
  - Cortisol replacement (hydrocortisone)
  - Aldosterone replacement if necessary (fludrocortisone)
  - Adequate suppression of androgen production, preservation of adult height, and prevention of adrenal crisis when ill
  - Normal female internal anatomy, good prognosis for fertility, with appropriate GU surgery

46, XY DSD

- Disorder of gonadal development
  - Partial/complete gonadal dysgenesis
  - Ovotesticular DSD
- Disorder in androgen synthesis/ action
  - Enzymatic defects impairing androgen synthesis
  - Receptor defects impairing androgen action
  - LH receptor defects/ Disorders of AMH
- Other
  - Severe hypospadias, cloacal extrophy, chromosomal anomalies
Androgen Insensitivity Syndrome

- Mutation of Androgen Receptor (Xq 11-12) a nuclear receptor
- CAIS: Female external genitalia, gonads in inguinal/abdominal position, hypoplastic Wolffian structures, absent Müllerian structures
- PAIS: Variable, management

CAH: Undervirilization in 46, XY

Sex Chromosome DSD

- Turner Syndrome
- Klinefelter syndrome
- Ovotesticular DSD
- Variable, with both ovarian/testicular tissues often ambiguous
- > half are 46XX, a third 46XX/46XY

Evaluation of the Neonate

- Refrain from gender assignments or other comments based on genitalia alone
- Detailed history
  - Family history, consanguinity, infant deaths, maternal ingestions, prenatal course
- Physical exam
  - Detailed genitalia exam, virilization, symmetry
- Diagnostic tests
  - Karyotype, ultrasound, 17 OHP Progesterone, etc.

Complete Leydig cell hypoplasia (LHCR defects)

- Scarcity of testosterone, leads to failure of intrauterine/pubertal virilization
- Female sex assignment
- Wolffian structures predominate
- Undescended testis
Gender Assignment and Long Term Outcomes

- Mid 1900s: Sex assigned appropriately if genitalia were constructed during infancy with subsequent upbringing corresponding to that sex
  - 14 (5-16 yrs) 46 XY patients assigned female sex at birth after repair of cloacal extrophy
    - In F/U (34-98 mo) 6 identified as male, 5 as female, 3 unclear (though 2 male at prior point)
    - All had moderate-marked interests and attitudes typical of male

5α-reductase-2 deficiency

- Inability to convert testosterone to DHT
  - Genital ambiguity at birth, though will masculinize with puberty

Dominican Republic (first noted in 1970s)

- Had been raised as girls, most transitioned to male gender (14 to 24 years), adapted well, often male-typical jobs, married females

Sambian tribe in New Guinea

- Historically raised as female, incorporated in tribal culture as men at puberty
  - Now when recognized at birth, raised as boys

Support Group/References

http://www.accordalliance.org (all DSDs)
http://www.caresfoundation.org (CAH)
http://www.aidsds.org (women with CAIS and other DSDs)
http://heainfo.org (hypoplasdias and epispadias)
http://www.aboutkidhealth.ca/En/HowTheBodyWorks/ SexDevelopmentAnOverview/SexualDifferentiation

Gender Assignment

- CAIS, 46 XY assigned female at birth
  - Most do not experience gender dysphoria
- PAIS, androgen biosynthetic defects, incomplete gonadal dysgenesis
  - 25% dissatisfaction with sex of rearing
- Ovotesticular DSD/ Mixed Gonadal DSD
  - Fertility capacity, phallic development, gonadal location

46 XX DSD: CAH

- Vast majority raised as girls and develop and maintain gender identity across the lifespan
  - However more common to note:
    - Less strong female identification
    - Masculine gender-role behavior
    - Gender discomfort
    - Gender dysphoria
- Generally, women with DSD:
  - Fewer relationships
  - More frequent psychological/psychiatric conditions