

An approach to infants and adolescents with Disorders of Sex Development (DSD)*

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*Formerly known as...

“The Approach to Intersex Disorders”

Outline

- “DSD”: a new nomenclature
- Normal sexual development
- An approach to the newborn and child with genital anomalies
- Focus on several DSD conditions

Why change the nomenclature?

- Prior terminology vague and stigmatizing:
 - **Intersex**-used in too many different ways
 - **Sex reversal**-unclear
 - **Hermaphrodite**-stigmatizing
 - **Pseudohermaphroditism**-unpronounceable
- Progress in diagnosis, surgical techniques, and understanding of psychosocial issues
 - Patient-centered care: multidisciplinary team approach
 - Psychological support and open communication: patient advocacy
 - More cautious surgical interventions



Consensus statement on Management of Intersex Disorders: Chicago, October 2005
 (50 international experts organized into work groups to develop consensus)

Definition: “Disorders of Sex Development (DSD)”



Congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical

Proposed changes

Previous	Proposed
Intersex	DSD
Male pseudohermaphrodite, undervirilization of an XY male, and undermasculinization of an XY male	46,XY DSD
Female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female	46,XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

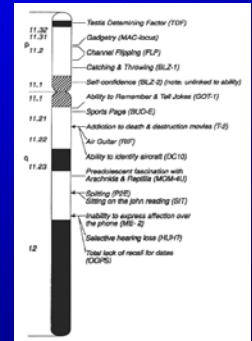
Lee, PA, Houk, CP, et al. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. *Pediatrics* 2006;118(2):e488-500.

Examples of DSD

- Sex chromosome DSD:
 - Turner syndrome
 - Klinefelter syndrome
- 46,XY DSD:
 - Gonadal dysgenesis
 - Androgen insensitivity syndrome (AIS)
- 46,XX DSD:
 - Congenital adrenal hyperplasia
 - Müllerian /vaginal anomalies

Normal sexual development

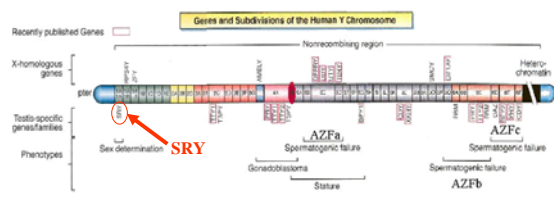
It all starts with the Y chromosome...



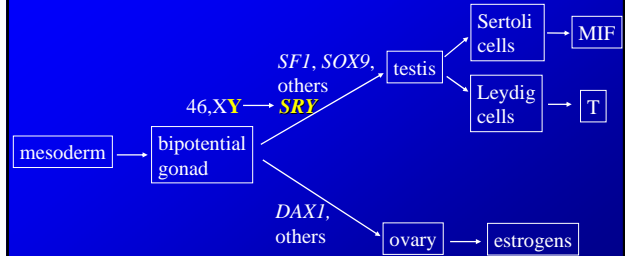
The Y chromosome

A Functional Map of the Y Chromosome

(from Lahn & Page 1997, Science 278:675)

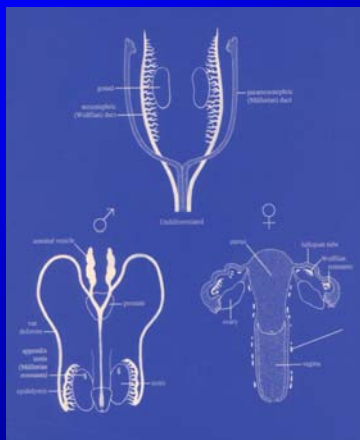


Normal sexual differentiation



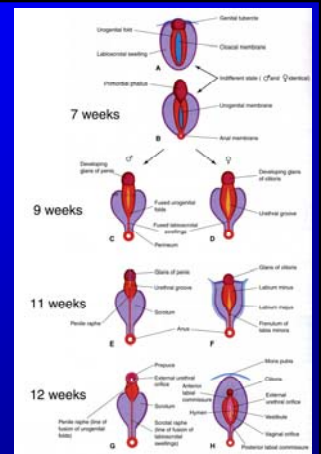
Differentiation of Internal Genitalia

- Undifferentiated structures at 8 wks gestation
- Testosterone induces Wolffian ducts (epididymis, vas, seminal vesicles)
- MIF (Müllerian Inhibitory Factor) causes regression of uterus and fallopian tubes

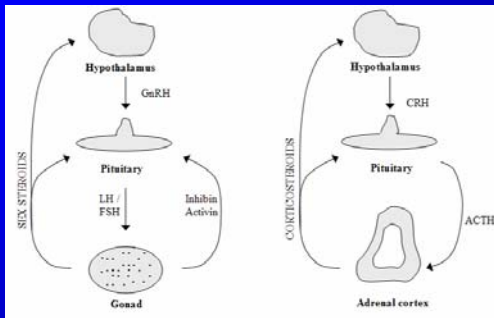


Differentiation of External Genitalia

- Undifferentiated gonad at 8 wks gestation
- Testosterone and DHT produced by embryonic testis
- Formation of external male structures by 13 wks!
- Growth of penis and external genitalia 14 wks-term
- Descent of testes into scrotum 7 mos-term



The endocrine system: hypothalamic-pituitary-gonadal/adrenal axis



The Brain is a sexual organ: the most poorly understood

- *Gender identity* = sense of self as a boy or girl
- *Gender role* = preferential adoption of behaviors more frequently observed in males vs. females
- *Sexual orientation* = preferred sex of partner e.g. heterosexual, homosexual, bisexual

These are not all the same!

An approach to the newborn and child with genital anomalies

The emergency situation... Newborn with ambiguous genitalia

Examples:

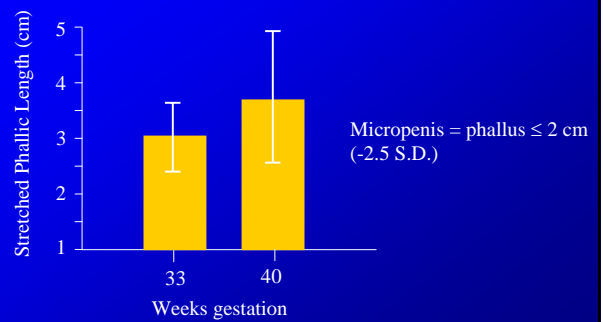
- Hypospadias with no palpable gonads
- Hypospadias with one palpable gonad
- Micropenis with no palpable gonads

Undermasculinized male (46,XY DSD)

- **Hypospadias:**
when the urethral opening does not extend to the tip of the penis

severity depends on the location
- **Cryptorchidism:**
undescended testicles
usually occurs in 3rd trimester of development

Penis length in a normal newborn male



The Team approach: urgent situations (newborns with ambiguous genitalia)

- If stable, bring to central institution for evaluation
- Specialists meet with family within 2 days
- No discussion regarding gender assignment with family before team meets
- Group conference is ideal, with family present
- Gender assignment made as soon as possible
- Hormonal profile at 2-4 months of age is important in newborns (“mini-puberty”)
- Close followup at 2-4 weeks, 8 weeks, and beyond
- Provide resources and support group information throughout

In the Delivery Room: recommendations for talking to parents

- Tell parents: “The sex of the baby cannot be determined yet.”
- Refrain from assigning gender: admit the infant as “Baby” Lastname
- Refer to the infant as “the baby” or by name if parents have chosen one
- Let them know that the baby has a difference in the formation of the genitalia, similar to babies born with a heart defect or cleft lip
- Assure them that doctors familiar with these issues will be meeting with them and that they will be involved in the process

<http://www.dsdguidelines.org>

Purpose of Gender Assessment (DSD) Team

- Diagnosis
 - Clinical
 - Surgical
 - Laboratory
 - Molecular
- Management
 - Medical
 - Surgical
- Genetic counseling
 - Recurrence Risks
 - Other family members
- Psychosocial/support
 - Parents
 - Patients

DSD Team Participants

- Medical Genetics
- Pediatric Urology
- Pediatric Endocrinology
- Gynecology
- Pediatric Psychology
- Cytogenetics
- Social Work



The Team approach: non-urgent situations

- Triage system with point person-Genetic counselor
- Consults are seen by all appropriate specialists at one time or within a few weeks in outpatient setting
- Discussion with family held after healthcare team has gathered information and conferred
- On-going care: regular followup with referrals to appropriate subspecialists
- Primary care physicians involved
- Team conference every 2 months:
 - Short-term issues: diagnosis and management
 - Long-term issues: longitudinal followup of patients

The Seattle experience over 25 years: 1981-2005

250 patients evaluated

On average, 10-15 new patients/year

- | | |
|--|-----|
| • Infants | 76% |
| • Children/Adolescents | 17% |
| • Known multi-system genetic syndromes | 7% |

Gender Assessment Team

Diagnostic Approach

Multiple malformations

Syndrome identification:

- Multiple congenital anomaly syndrome
- Autosomal chromosomal abnormality
- Exstrophy of the cloaca

Isolated genital abnormality

Determination of:

- Chromosomal sex
- Gonadal sex
- Phenotypic sex

GOAL

- Chromosomal sex
 - Gonadal sex
 - Phenotypic sex
- Parental input

Sex of Rearing



Timing: As soon as possible based on best information

History

- Maternal: androgen effects, exogenous fetal androgen exposure
- Past Medical: use of androgens, growth pattern, menarche
- Family: infertility, genital abnormalities, genital surgery, multiple miscarriages, consanguinity

Physical Exam

- Measurement of genitalia
 - Micropenis: <2 cm
 - Clitoromegaly: >1 cm
- Gonad palpation
- Evaluate for multiple congenital anomalies

Gonadal Evaluation

- **Physical Exam:** Descended/palpable gonad = testicular tissue
- **Pelvic ultrasound:** Müllerian structures = no MIF
- **Laparoscopy, laparotomy:** Gonadal biopsy

Genetic Evaluation

Karyotype

- >20 metaphases for mosaicism, structural abnormalities
- 24, 48, 72-hr harvest

FISH

- Presence of SRY
- X and Y probes for gonadal biopsies

Specialized molecular genetic tests

- Mutation analysis of 21-hydroxylase gene
- Androgen receptor sequencing
- Y chromosome microdeletions

Endocrinologic Evaluation

- Hypothalamic/pituitary/gonadal Axis:
Gonadotropins: LH, FSH
Gonadal response: Testosterone, DHT, estrogen
- Adrenal function:
Electrolytes, 17-OH-P
DHEAS
Cortisol
- Response to challenges:
GnRH stimulation
HCG stimulation
T stimulation

Internal genitalia

- Newborn:
Pelvic ultrasound for Müllerian structures, +/- gonads
Cystoscopy
- Older Child:
MRI vs. laparoscopy / laparotomy, +/- gonadal biopsy

Psychological Evaluation

- Family's concerns and wishes:
Desired gender of child
Cultural/religious/family values
Sexual function
Potential for fertility
- Gender identity: ????
- Gender role: ????
- Sexual orientation: ????

Psychosocial Implications: Working with Families

- Assign sex with understanding that child may make a different decision later in life
- Postpone surgical interventions if possible until child is old enough to participate in decision making
- Importance of team approach, full disclosure, ongoing education and support for patients and families

<http://www.dsdguidelines.org>

General guidelines for gender assignment

- Try to match the baby's sex assignment to the chromosomal and gonadal sex if possible
- Try to anticipate pubertal development
- Consider future function when planning surgeries
- Try to preserve fertility
- Respect the opinions of well-informed parents vs. allowing the child to decide as an adult (controversial)

The Seattle experience: 6 most common diagnoses

- | | |
|------------------------------------|------------|
| • Congenital adrenal hyperplasia | 12% |
| • Androgen insensitivity syndrome | 10% |
| • Clitoromegaly / labial anomalies | 8% |
| • Mixed gonadal dysgenesis | 8% |
| • Hypogonadotropic hypogonadism | 8% |
| • 46,XY SGA males with hypospadias | 7% |
| • TOTAL | 53% |

Focus on several DSD conditions

- CAH
- AIS
- Turner syndrome
- Ovotesticular DSD
- Smith-Lemli-Opitz syndrome

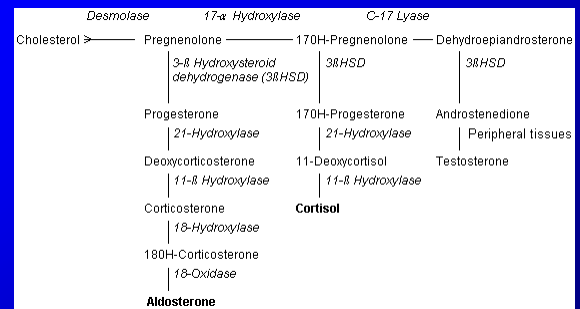
Congenital Adrenal Hyperplasia

- Incidence: 1/15,000 for classic form (1/300 in Yupik)
- Mild forms: 1/100-1/1000 (common !)
- Two types:
 - 75% are classic salt-wasting
 - 25% are simple virilizing
- Clinical features in infancy:
 - Virilized female without palpable gonads
 - Male with precocious puberty
 - Salt-wasting crisis in first month
- Endocrine testing:
 - Elevated **17-OHP** (KEY!)
 - Abn. electrolytes (low Na, high K)
 - Elevated androgens
 - Elevated renin if salt-wasting form

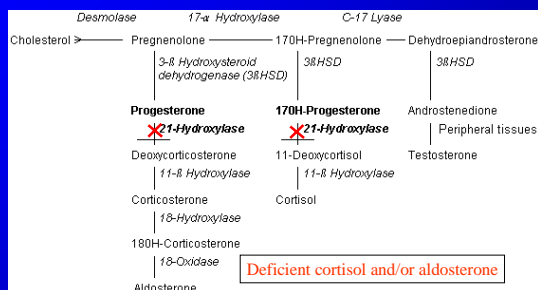
Genetics of CAH

- Autosomal recessive inheritance
- Etiology:
 - 90% due to 21-hydroxylase deficiency
 - 5% due to 11-beta-hydroxylase deficiency
 - Other rare enzymes involved
- Genetic testing of *CYP21* gene:
 - 9 common mutations found in 90-95%
 - Phenotype variable depending on mutation
 - Advisable to test parents if possible—may have mild form of CAH

Adrenal hormone pathway



Adrenal hormone pathway with 21-hydroxylase deficiency



Treatment in CAH

- Treat adrenal crisis: oxygen, fluids, glucose, replace hormones
- Lifelong hormone replacement
 - Cortisol and flornief, +/- salt
 - Need extra cortisol at times of stress, infection
- Monitor for puberty, during pregnancy
- Surgery in females may include:
 - Feminizing genitoplasty and clitoral recession in infancy (6-18 months)
 - Vaginoplasty in late teens

Recommended management in at-risk pregnancies

- Treat pregnant women at 25% risk of recurrence with:
 - Pre-pregnancy genetic counseling and testing
 - By 10 wks gestation, start high-dose dexamethasone in mother to prevent virilization in female fetuses
 - CVS at 10-12 wks or amnio at 15-20 wks
 - Stop treatment if fetus is male or genetic testing indicates the female fetus is unaffected

Androgen Insensitivity Syndrome (AIS)

- Incidence: ~1/20,000
- Features: 46,XY karyotype with undermasculinization
- Presentation - the 3 major forms:
 - Complete form (CAIS): phenotypic female with inguinal gonads (infancy) or pubertal failure
 - Partial form (PAIS): variable degree of masculinization
 - Mild form (MAIS): undervirilized male, impaired spermatogenesis

Really, a spectrum!



Complete AIS



- Clinical features in CAIS:
 - No Müllerian structures (MIF is produced in utero)
 - Female breast development, blind vagina, absent pubic and inguinal hair, often tall for women
 - Elevated T levels for a female (normal for male)
 - Identify as female

Androgen Insensitivity Syndrome (AIS)

- Etiology: X-linked recessive
 - Mutations in the androgen receptor (*AR*) gene in >95% of CAIS; ? yield in PAIS
 - Failure to respond to male androgens (T, DHT)
- Treatment in CAIS:
 - Remove inguinal hernias
 - Gonadectomy before or immediately after completion of puberty (increased risk of gonadoblastoma)-debated
 - Estrogen replacement
 - Vaginal reconstruction or vaginoplasty may be needed
 - Supportive counseling for infertility
 - Genetic counseling for family members
- Sex assignment in PAIS:
 - Can be very challenging—how will a child virilize at puberty?

Infant with PAIS

Genetic defect:
missing part of exon 1 of *AR* gene

2 months

Birth:

Bilateral cryptorchidism
Penoscrotal hypospadias
No Müllerian structures
T=234 ng/dl (high)
LH, FSH elevated

Turner syndrome (TS)

- Prevalence:
 - 1:150 conceptions
 - 1:2500 live female births
 - 1:50 girls below 2nd % in height
- Classical Signs

	reason for Dx in:
– Congenital lymphedema	1/3
– Short stature	1/3
– Pubertal failure	1/3

Congenital lymphedema



Redundant nuchal skin in Turner syndrome



TS: clinical features

- Short stature
- Facial features
 - Variable ptosis, epicanthal folds
 - Lowset, posteriorly rotated ears
 - Webbed neck
- Hearing loss
- Body habitus
 - Broad chest with widely spaced nipples
 - Increased carrying angle at elbows
 - Short 4th and 5th metacarpals
 - Scooped nails

Other clinical features in TS

- Cardiac
 - Bicuspid aortic valve; coarctation of aorta; hypertension
- CNS (<10% have MR)
 - Difficulty with spatial relationships, math skills
- Endocrine
 - Type II diabetes; hypothyroidism (almost 1/3 of adults)
- Renal (40%)
 - Duplication, horseshoe kidney, hydronephrosis
- Fertility
 - Gonadal dysgenesis-treat with hormone replacement
 - If Y chromosome material, risk of gonadoblastoma
 - Pregnancies reported in some but inc risk of aneuploidy

Clinical Appearance in TS



Most common karyotype in TS: 45,X



Not all girls with TS have classical features



A Teenager with Turner syndrome



An elderly woman with Turner syndrome



Ovotesticular DSD: 45,X/46,XY or 46,XX/46,XY

Ovotesticular DSD

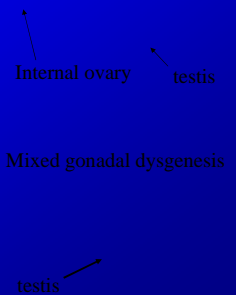
•Mosaic or chimeric condition

•46,XX/46,XY with genital ambiguity- have ovary and testis or ovotestis (formerly "true hermaphrodite")

•When 46,XX/46,XY is detected in utero, often newborn is normal male

•45,X/46,XY can be Turner syndrome or mixed gonadal dysgenesis

•Need to remove gonads if female with Turner syndrome and Y chromosome material



Smith-Lemli-Opitz syndrome



Smith-Lemli-Opitz syndrome (SLOS)

- Incidence: 1/20,000 live births
- Clinical features:
 - Poor growth, FTT, and microcephaly
 - Unique facial features
 - GU: Cryptorchidism, hypospadias, micropenis
 - Mod-severe MR
 - Heart defects, holoprosencephaly, clefts
 - 2-3 toe syndactyly, polydactyly
- Etiology:
 - Autosomal recessive
 - 7-dehydrocholesterol reductase gene (*DHCR7*)
 - Diagnosis: elevated 7-DHC, low cholesterol



Toes in SLOS

Postaxial polydactyly

2-3 syndactyly

Older child with SLOS



Resources

- Clinical guidelines and parent handbook for management of disorders of sex development in childhood: www.dsdguidelines.org
- Hospital for Sick Children genital development web page: www.sickkids.ca/childphysiology/cpwp/Genital/GenitalIntro.htm
- Intersex Society of North America: www.isna.org
- AIS support groups: www.aissgusa.org, www.medhelp.org/www/ais/
- Hypospadias/epispadias association: www.heainfo.org
- Seattle Children's DSD Team:
 - Melissa A. Parisi, MD (206-987-2689) mparisi@u.washington.edu
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Acknowledgments

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