

Disorders of Sexual Differentiation (DSD): History, Evaluation and Controversy

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Hermaphroditus

Theophrastus

3rd century BC

The Characters,

XVI The Superstitious Man

Ancient Cultures and DSD

- Sumerian:

- *Ninmah*, a mother goddess created humanity from clay
 - Created 6 humans. #6 had both a penis and vagina



- Judaism

- ...either androgynos or tumtum (hidden) ... different gender roles
...male sometimes female.



- Islam

- Arabic as *khuntha* (all disorders)...sex could be determined by site of urination in a practice called *hukm al-mabal*... no identifiable sex organs, was assigned the intermediary sex category *khuntha mushkil*

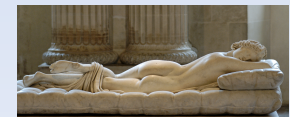
- South Asia

- *Hijra*, 3rd sex category



- Greece:

- Hippocratic/Galenic model...masculine men, feminine women, and many shades in between....including hermaphrodites...a perfect balance of male and female



History of DSD

Middle Ages: "If someone has a beard, and always wishes to act like a man (exercere virilia) and not like a female, and always wishes to keep company with men and not with women, it is a sign that the male sex prevails in him and then he is able to be a witness, where a woman is not allowed."

Early Modern Period: Edward Coke (Lord Coke), wrote in his *Institutes of the Lawes of England* ... "Every heire is either a male, a female, or an hermaphrodite, that is both male and female. And an hermaphrodite...shall be heire, either as male or female, according to that kind of sex which doth prevaile."

Mid Modern Period: Victorian medical authors introduced the terms "**true hermaphrodite**" (both ovarian and testicular tissue), "**male pseudo-hermaphrodite**" (testicular tissue, but female/ambiguous sexual anatomy), and "**female pseudo-hermaphrodite**" (ovarian tissue, but either male/ambiguous sexual anatomy)

History of DSD

1917: Goldschmidt >> Intersex

1950: John Money >> “Optimal Gender Policy”

1930-1960s: Hugh Hampton Young: Pioneered Genital Reconstructive Surgery

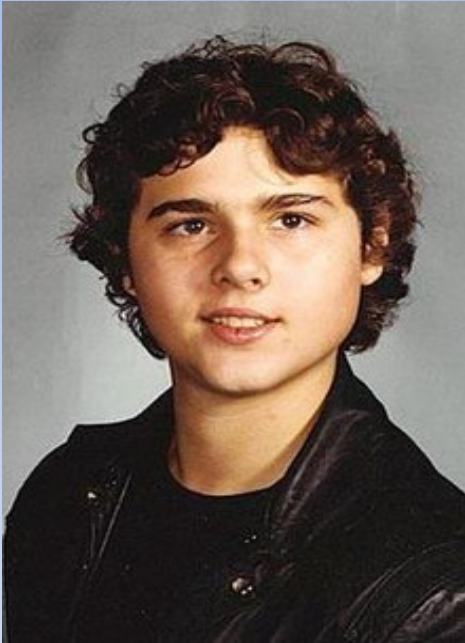
1970-1980s: Surgery Sex Reassignment uncritically accepted in academics and society at large

1980s: Began to understand Sex Hormones are important in sexual behavior and gender identity

1990s: Culture is not important in human sexual behavior.
Biological factors are important

1996: American Academy of Pediatrics : Supports Surgery: Sex assignment can determine sex identity if performed < 2.5 years

History of DSD



1997 David Rimmer

1999: Columbia, SA: Limited the ability of parents to consent to genital surgery for infants with intersex conditions

2006: Intersex >> DSD

2014: WHO: 81% of 439 patients with intersex underwent surgery >> 50% had psychological issues >> 66% felt surgery was the reason for issues with family life and physical well being

2015: Malta outlawed non-consensual modifications to sexual characteristics

2016: Global Disorders of Sexual Development Update: Timing and choice of individual and irreversible surgical procedures are sources of concern....Physicians should... emphasize preserving patient autonomy.

2018: California State Legislature passed a resolution condemning surgery

What is DSD

DSD: altered physical sex differentiation



Incidence Rate

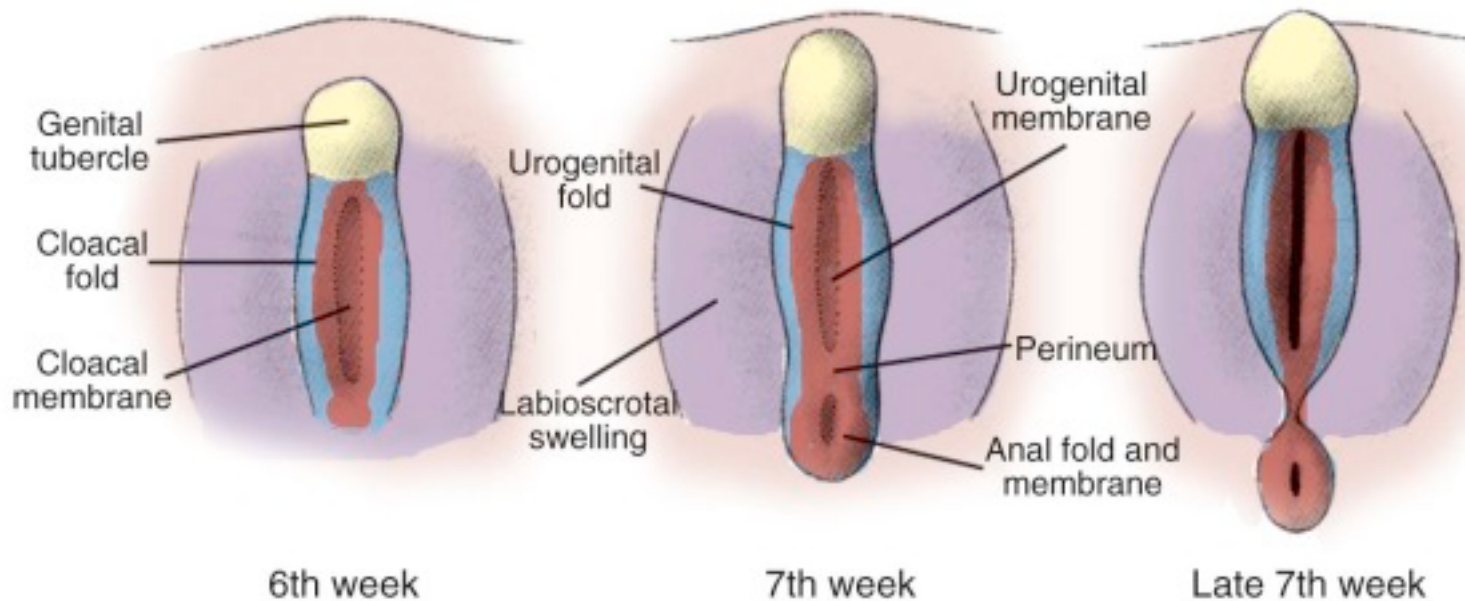
46 XY DSD 1/20,000 births

46 XX DSD 1/14,000-15,000 births

Mixed Gonadal Dysgenesis 1/10,000 births

Normal Genital Development

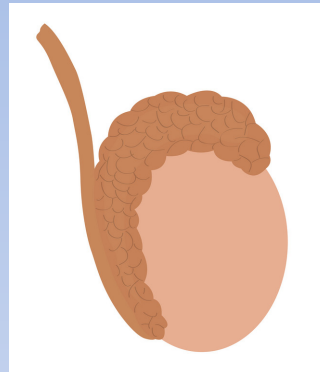
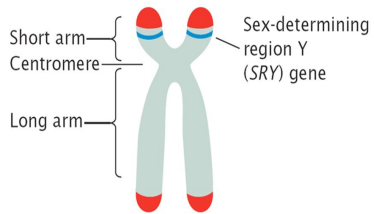
A. Indifferent stage



Normal External Genital Development: XY

SRY Gene

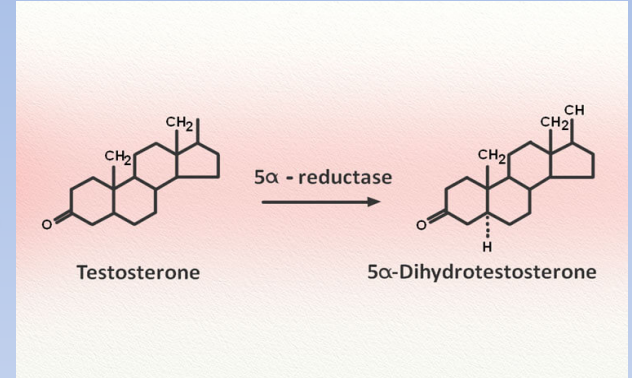
- Only on Y Chromosome
- Upregulates Sox9



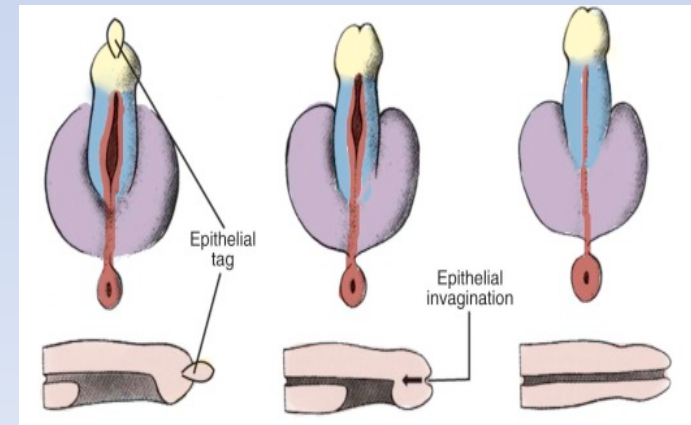
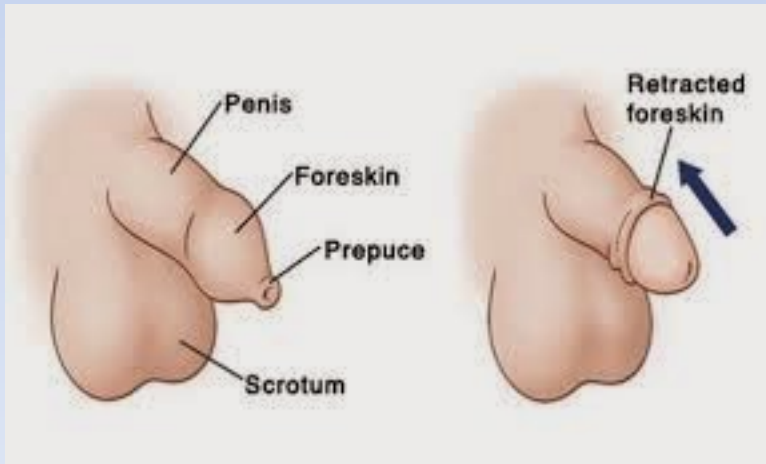
Leydig cells



Sertoli cells



Anti-Müllerian hormone



Normal Internal Genital Development: XY

Leydig Cells



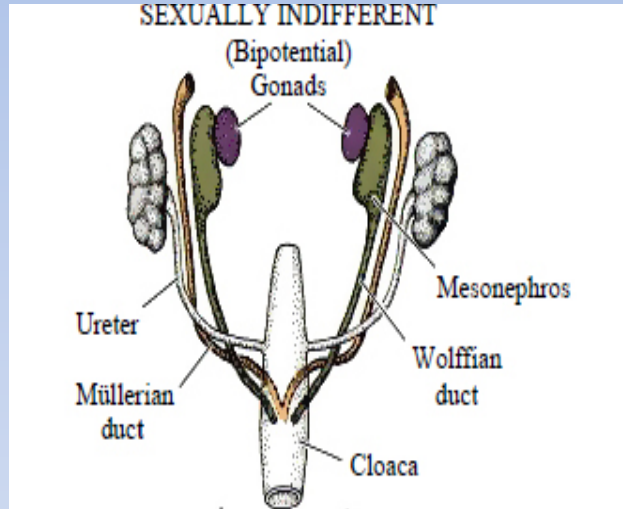
Testosterone
Insulin-like 3



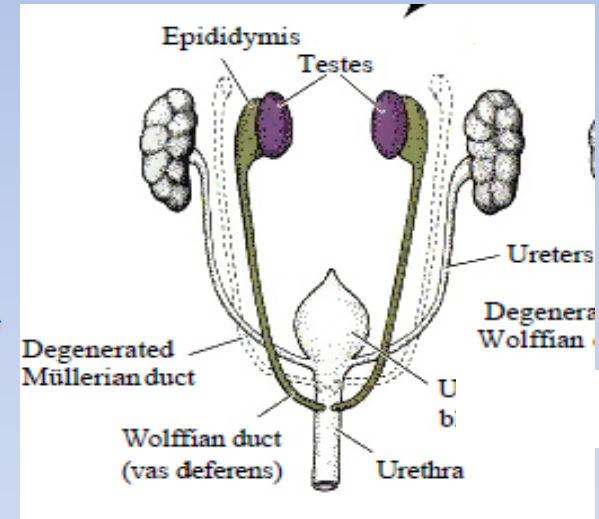
Sertoli cells



Anti-Müllerian
hormone

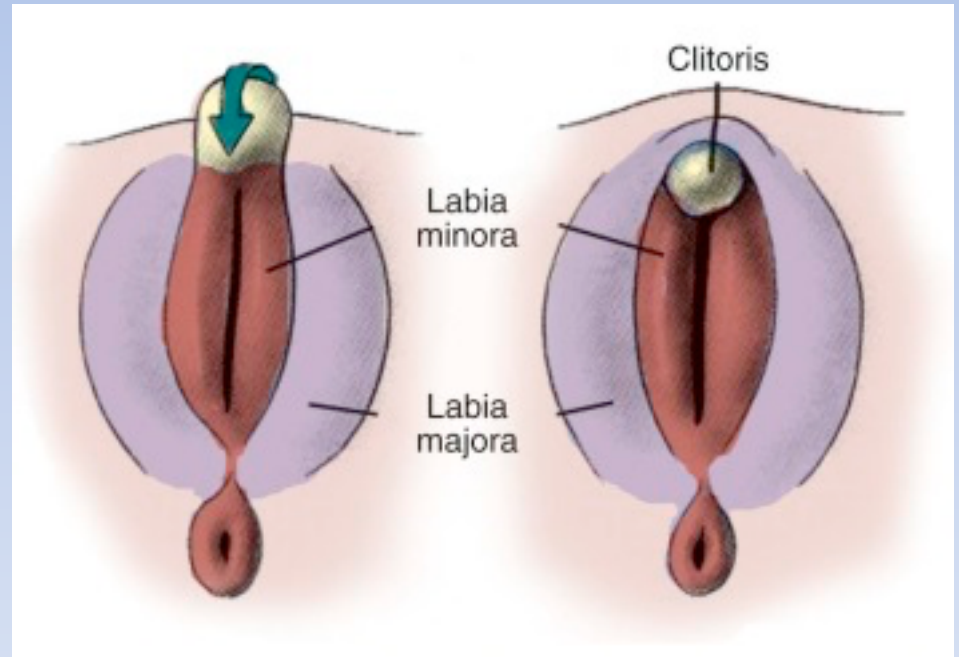
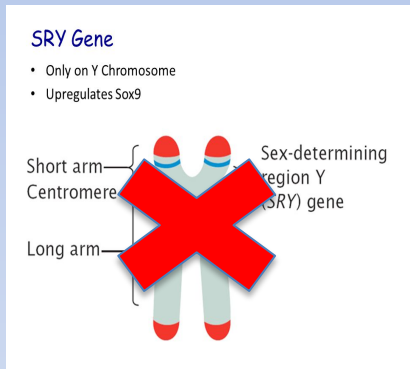


Testicular Descent
to Scrotum



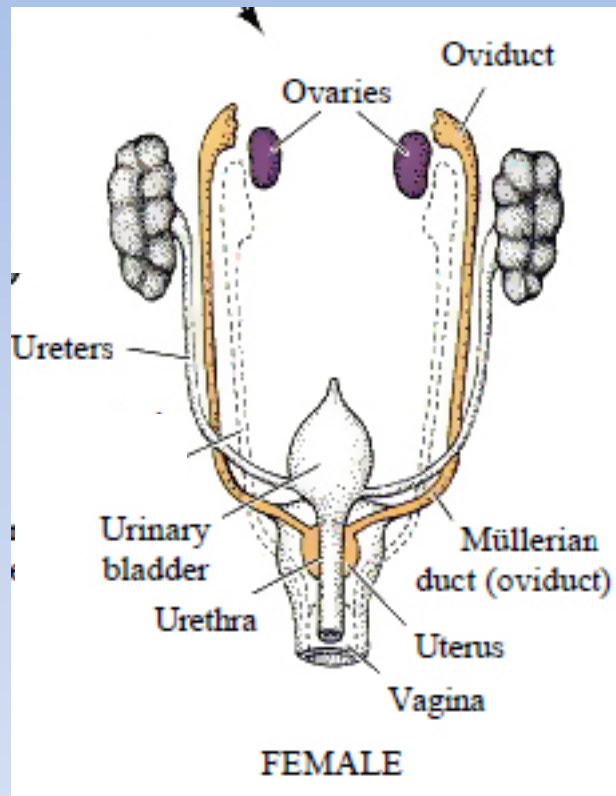
Epididymis
Vas deferens
Seminal vesicle
Ejaculatory Duct

Normal External Genital Development: XX



Normal Internal Genital Development: XX

Leydig ~~Cells~~
↓
Testosterone ~~Insulin-like 3~~
↓
Sertoli ~~cells~~
↓
Anti-Müllerian ~~hormone~~



Gonads do not
descend

Uterus
Fallopian Tubes
2/3 Upper Vagina

Ambiguous Genitalia



True Hermaphrodite

Classification of DSD

- 46 XY DSD (Male Pseudohermaphrodite)
 - Defects in Testicular Development
 - Denys-Drash Syndrome
 - WAGR syndrome
 - XY pure gonadal dysgenesis
 - Deficiency of Testicular Hormones
 - Leydig cell aplasia
 - Lipoid Adrenal Hyperplasia deficiency
 - 3 β HSD II deficiency
 - 17-Hydroxylase/17,20-lyase deficiency
 - Defect in Androgen Action
 - 5 α -reductase II deficiency
 - Androgen insensitivity Syndrome (AIS)

Classification of DSD

- Ovotesticular DSD (True Hermaphrodite)
 - XX
 - XY
 - XX/XY chimeras
- Sex Chromosome DSD
 - 45X (Turner Syndrome and variants)
 - 47 XXY (Klinefelter Syndrome and variants)
 - 45 X/46 XY (mixed gonadal dysgenesis, sometime cause of ovotesticular DSD)

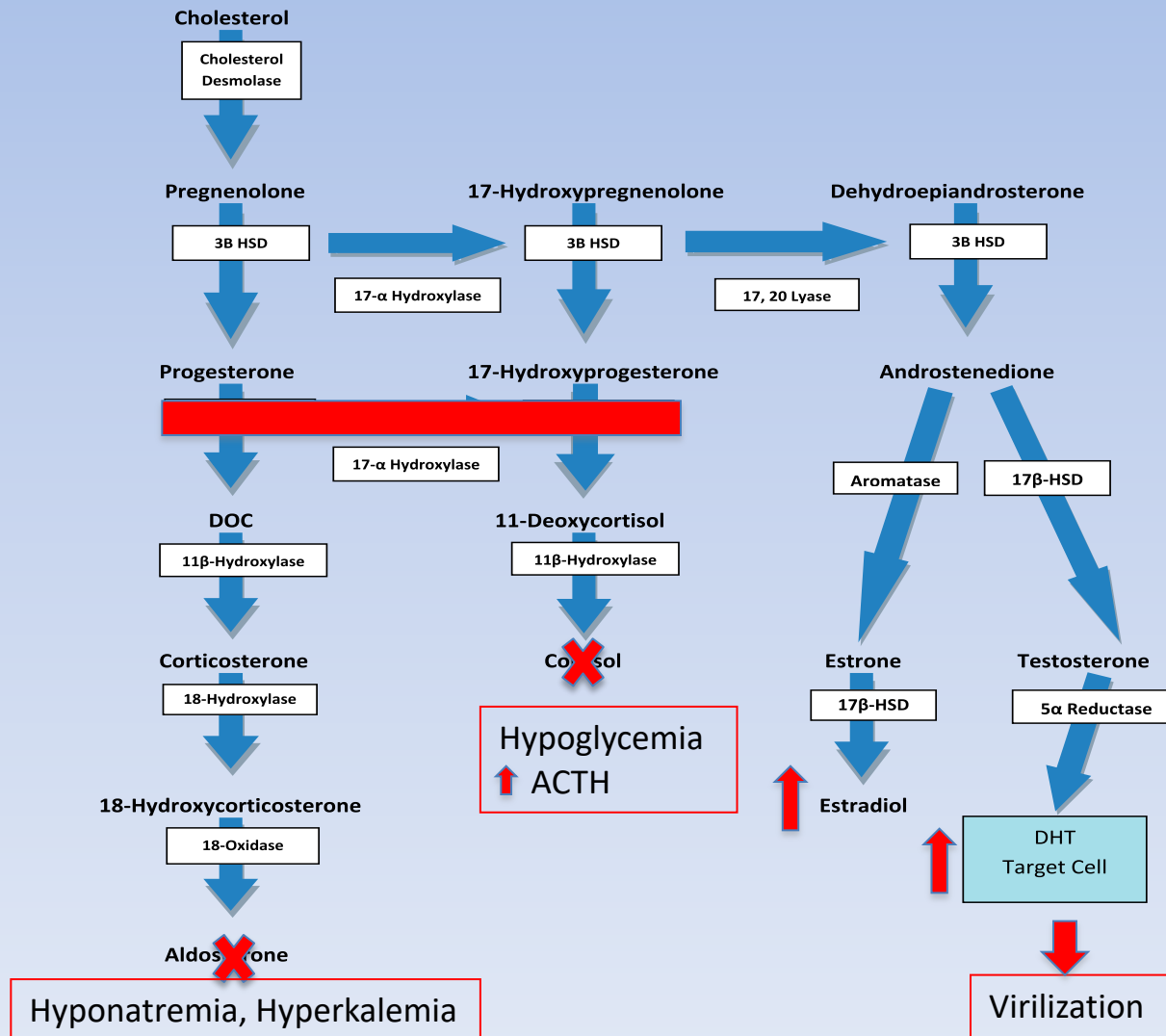
Classification of DSD

- 46 XX DSD
 - Androgen Exposure
 - 21-Hydroxylase deficiency
 - 11 β -Hydroxylase deficiency
 - 3 β -Hydroxysteroid dehydrogenase II deficiency
 - Aromatase (P450 arom or CYP19) deficiency
 - Glucocorticoid receptor gene mutations
 - Virilizing tumors
 - Androgenic drugs
 - Disorders of Ovarian Development
 - XX gonadal dysgenesis
 - Testicular DSD (SRY+, SOX 9 duplication)
 - Other

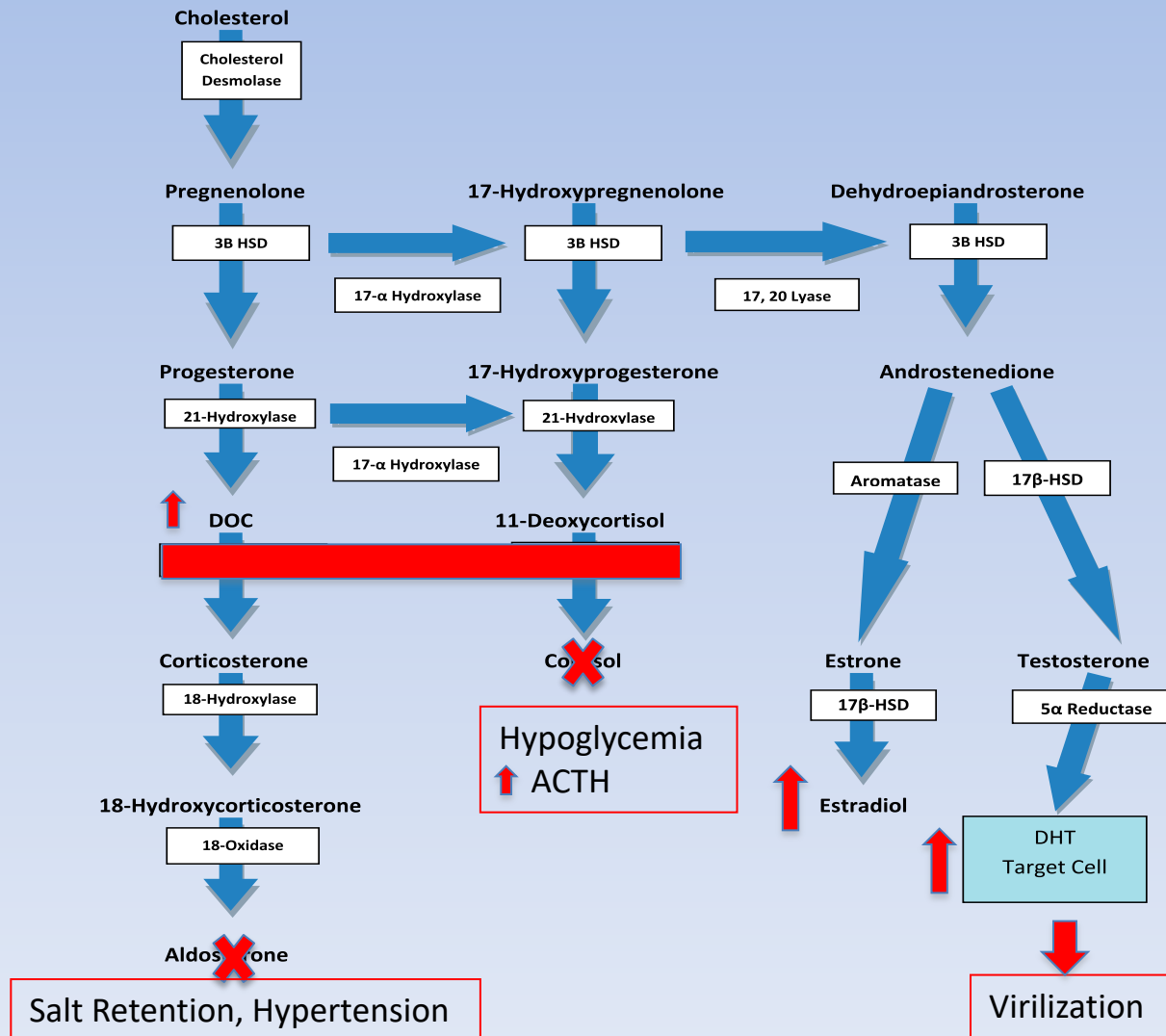
Congenital Adrenal Hyperplasia (CAH)

- 46 XX DSD
 - 21 α -Hydroxylase deficiency
 - 11 β -Hydroxylase deficiency
 - 3 β -Hydroxysteroid dehydrogenase deficiency
- 46 XY DSD
 - 3 β -Hydroxysteroid dehydrogenase deficiency
 - 17 Hydroxylase/17,20-lyase deficiency

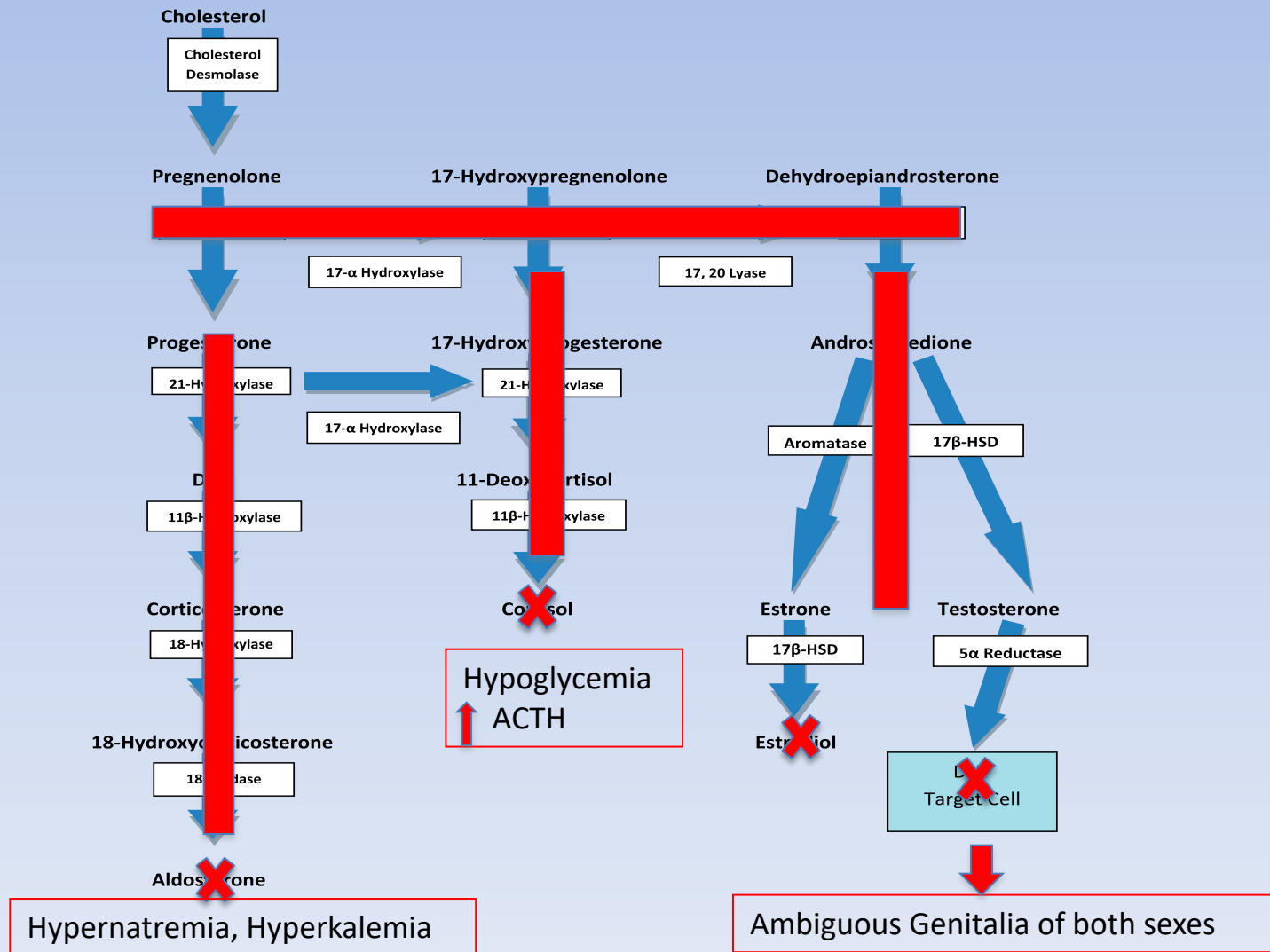
21-Hydroxylase Deficiency



11 β -Hydroxylase deficiency



3 β -Hydroxysteroid dehydrogenase II deficiency

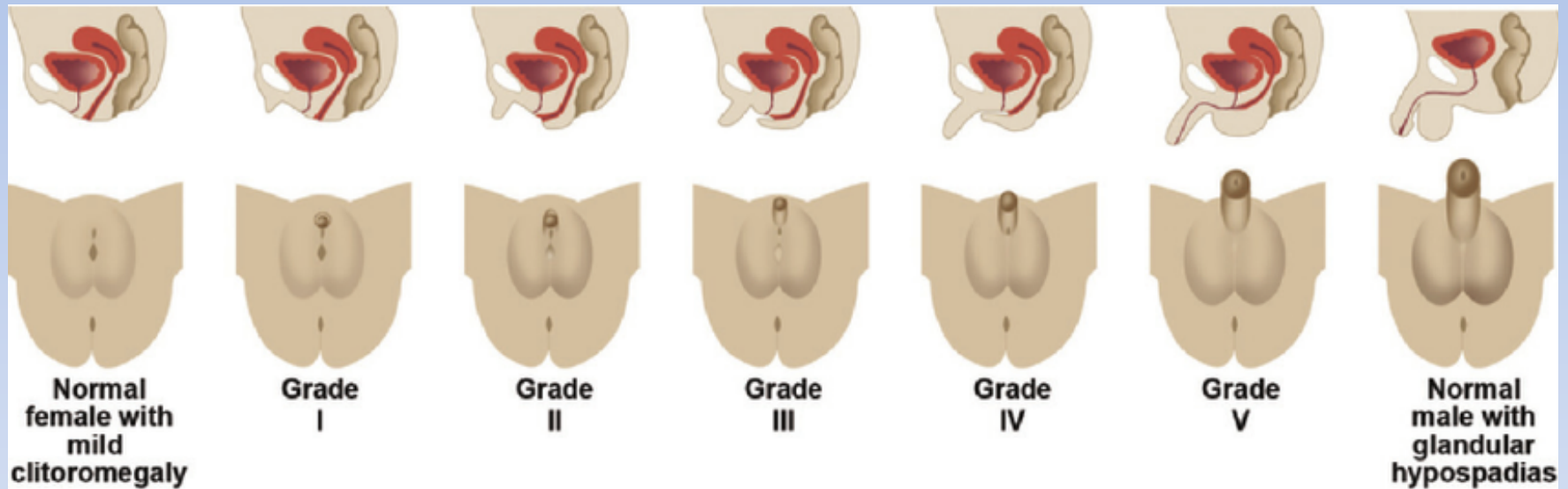


Clinical Investigation of Ambiguous Genitalia

- Prenatal History
- Family History
 - Consanguinity  Risk Autosomal Recessive disorder. Ex. CAH
 - Infant Death (Salt-Wasting CAH)
 - Ambiguous Genitalia
 - Urological anomalies
 - Female infertility/Amenorrhea
 - Maternal Drug Exposer
 - Maternal Virilization (maternal tumor)
- Medical and Developmental History
 - Adolescent Presentation

Clinical Investigation of Ambiguous Genitalia

Prader Scale




Labioscrotal hyperpigmentation
Gonads Palpable/Nonpalpable
Stretched phallic length (< 2.5 cm micropenis)
Phallic width
Degree of chordee

Late Presentation of DSD

- Primary Amenorrhea
- Progressive Virilization
- Delayed or Incomplete Pubertal Development

Clinical Investigation of Ambiguous Genitalia

- Chromosomal Microarray Analysis
 - 1st 24 hours
- Labs:
 - Chemistry
 - Glucose
 - 17-hydroxyprogesterone (unreliable < 36 hr)
 - Gonadotrophins (LH, FSH)
 - Testosterone
 - Anti-Mullerian Hormone ( Boys than Girls)

Interpretation of Labs

- 46 XX:
 - ACTH Stimulation Test
 - bHCG stimulation Test
 - ↑ 17-OHP and Androgen = CAH
 - ↑ AMH and Androgen = Ovotesticular DSD
 - ↑ Androgen and normal AMH = Aromatase Deficiency
 - ↑ Androgen decreases with time = Maternal source
- 46 XY:
 - ↓ Androgen and AMH = Dysgenetic Gonads
 - ↓ Androgen and normal/high = Steroid Defect
 - ↑ Androgens and AMH = Androgen Insensitivity

Clinical Investigation of Ambiguous Genitalia

- Radiology Imaging
 - Pelvic/abdominal Ultrasound
 - MRI
- Gonadal biopsy (some cases)
- Genitourinary Sinogram





Is it a boy or a girl?

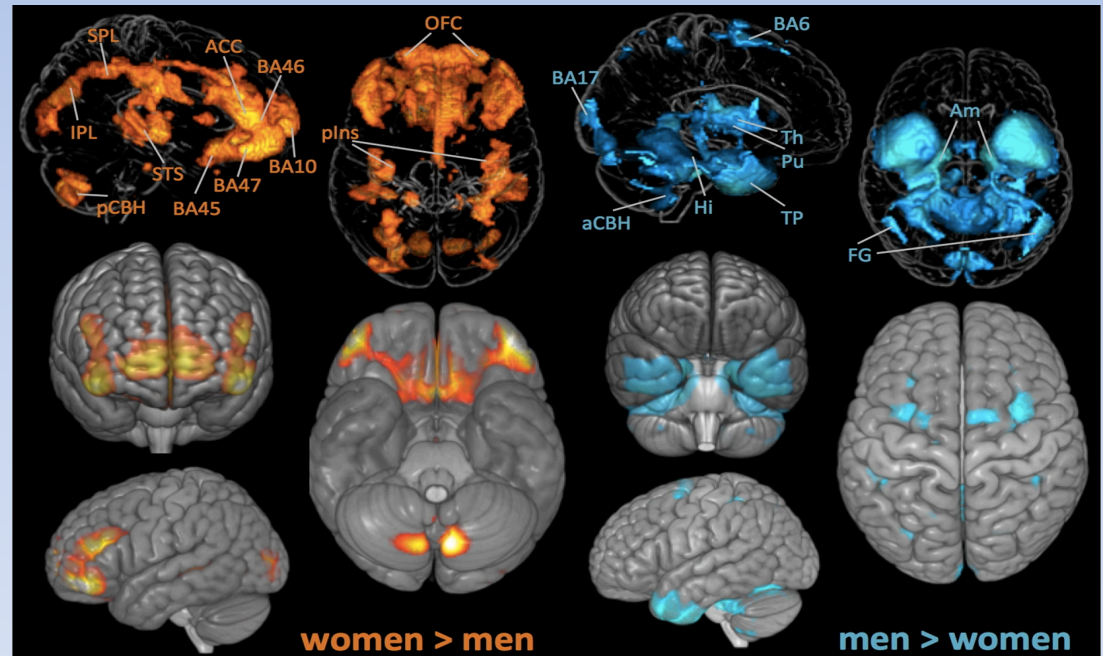
Determining Gender

- “Before the 1950s...infant gender based on its “true sex,” ... determined by biological findings ...external genitalia or karyotype
- 1950s and 1960s... infants were born *tabula rasa* (blank slate)...gender identity ...social and environmental influences

Determining Gender

- Differences between the male and female brain

- Imaging
- Morphology
- Histology

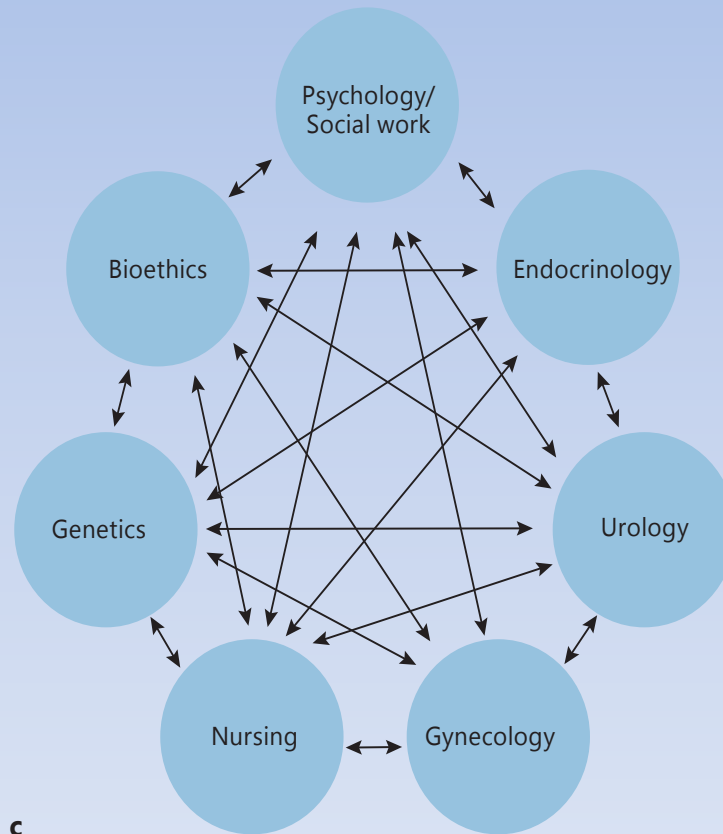


Grey matter varies between sexes when regions of the brain are compared

Determining Gender

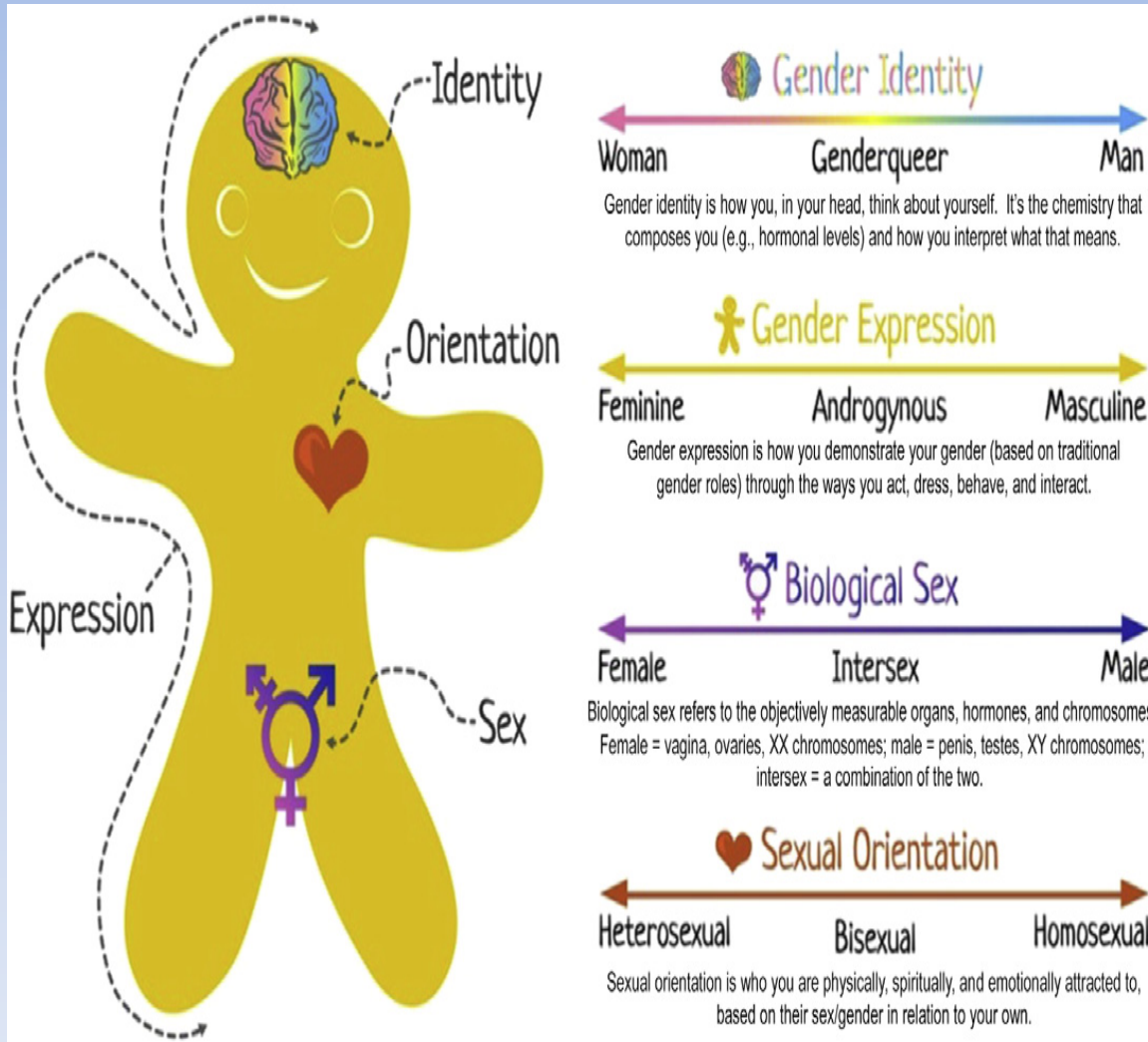
Hormonal Imprinting: Testosterone during a brief perinatal period enters the developing brain to act via androgen receptors or after aromatization to estrogen via estrogen receptors to induce sex differences

It takes a village.....



c

Educating Parents



Determining Gender

Parents will select Gender after they have been educated believing/hoping they are correct

In some cases, gender may not be assigned.

Goal: Gender Congruence

The feeling of harmony with ones gender

Surgical Intervention in DSD

The European Society of Pediatric Urology and Society for Pediatric Urology

“Atypically developed genitalia can affect not only physical appearance and body image, but also function of the urinary tract, kidneys, gonads, and the psychological and psychosexual development of the individual.

Therapeutic management of these patients is, therefore, not limited to ‘cosmetic’ surgery as stated in some reports. . . ”

Medical and surgical management aims were specified as: “Avoiding potential health hazards related to the altered anatomy and function of the urogenital tracts, meeting parents’ expectations and helping the individual to achieve future satisfactory sexual function, consistent with their gender identity. . . ”

Surgical Intervention

- Urgent Surgical Intervention
 - Obstructed Bladder
 - Obstructed Rectum
- Elective Surgical Intervention
 - Gonads
 - Internal Reproductive Anatomy
 - External Genitalia

Surgical Intervention

- Gonads
 - Cancer Risk
 - 30-50% : Dysgenetic Gonads with Y chromosome
 - 1-22% : Errors in Testosterone Action or Synthesis
 - Prevention Contrasexual change
 - Ex. Female to Male at puberty
 - Utilization of hormones at Puberty
 - Ex. Complete Androgen Insensitivity Syndrome
 - Testosterone>>> Estrogen>>> Breast Development
 - Gender Congruence
 - Can consider gonadotropin releasing hormone agonist

Surgical Intervention

- Fertility and DSD
 - 1030 patients > 32 years with DSD diagnosis
 - 99.3% were CAH with 0.7% other diagnosis
 - 33% had a partner
 - 14% had ≥ 1 child
 - 7% with ART
 - 4% adopted
 - 3.5% reproduced without ART

Table 1 Fertility summary in DSD.

Type of DSD	References	Fertility rate	Overall fertility and specifics
46,XX DSD (masculinized female)			
CAH			
21-hydroxylase deficiency			Reared female: fertility possible with hormonal replacement/treatment. Fertility rates: non-classic > simple masculinizing > classic salt wasting
Classic salt-wasting CAH	Claahsen-van der Grinten et al. [4]	0–10%	
Simple masculinizing CAH	Claahsen-van der Grinten et al. [4]	33–50%	
Non-classic CAH	Claahsen-van der Grinten et al. [4]	63–90%	
11 β -hydroxylase deficiency	Simm et al. [7]	1 case report	Subfertility: rare fertility with hormonal therapy
3 β -HSD deficiency		No reported cases	Infertile to date
CYP17A1 mutation	Marsh et al. [9], Levran et al. [10]	1 case report	Infertile: 1 case with IVF and frozen ET
46,XY DSD (undermasculinized male)			
CAH			
21-hydroxylase deficiency	Falhammar et al. [12]	~ 1/2 compared to national data controls	Fertility reduced in males; lower T/E2 ratio, higher FSH; abnormal semen parameters in ~50%; TARTs may play role and are treated with steroids
CLAH	Metherell et al. [15]	Cases reported	<i>Classical form</i> leads to complete sex reversal (infertile); <i>non-classical forms</i> with varied phenotype, fertility reported in males (subfertile)
3 β -HSD deficiency	Burckhardt et al. [16]	1 case report	Subfertile to infertile; testicular biopsies show spermatogenic arrest and Sertoli-only cells
POR deficiency	Fukami [17]	No reported cases	Infertile: delayed puberty common
Disorders of T biosynthesis			
17OH deficiency	Diamond and Yu [18]	No reported cases	<i>Complete form</i> often reared female with gonadectomy and estrogen replacement at puberty (infertile); <i>Partial form</i> require T replacement at puberty if reared male (infertile)
17 β -HOR deficiency	Auchus and Miller [19]	No reported cases	Infertile
Leydig cell hypoplasia/agenesis	Bakircioglu et al. [20]	1 case report	Infertility thought universal with azoospermia common; recently 1 case of life birth after ICSI with cryopreserved sperm from micro-TESE
Disorders of androgen target tissue			
Androgen insensitivity syndrome			
Complete AIS	Rutgers and Scully [21]	No reported cases	Reared female: absence of Müllerian structures (infertile); possibility of male fertility factor low
Partial AIS	Tordjman et al. [24]	Cases reported	Reared female: absence of Müllerian structures (infertile); Reared male: variable phenotypes and typical cryptorchidism histology; fertility possible spontaneously (hormonal treatment) or with IVF (subfertile)
Disorders of T metabolism			
5 α -reductase type 2 deficiency	Katz et al. [29], Kang et al. [30]	Decreased	Reared female: gonadectomy to prevent virilization (infertile); Reared male or male gender reassignment at puberty: orchiopexies and have oligoastheno-teratospermia, natural paternity rare but fertility possible with IUI and TESE/ICSI

Fertility rates (CAH) depend on phenotype and are inversely proportional to the severity of the disease.

Men with classic CAH have reduced fertility and due testicular adrenal rest tumors and to suppression of the hypothalamic-pituitary-gonadal axis by high systemic levels of androgens.

Persistent Müllerian duct syndrome	Josso et al. [32]	Extremely low	Azoospermia may be due to abnormal germ cell maturation and/or epididymal or ductal abnormalities; fertility possible with IVF
Disorders of gonadal differentiation			
Klinefelter syndrome	Ramasamy et al. [34]	~50% with TESE	Infertility the rule although cases of fertility now possible with TESE/ICSI
46,XX male	Vorona et al. [37]	No cases reported	Azoospermia and infertility universal
Syndromes of gonadal dysgenesis			
Turner syndrome	Hovatta [38], Karnis [39]	2-5% (spontaneously in mosaic forms)	Infertility due to premature ovarian failure; spontaneous pregnancy seen in mosaic forms; oocyte donation successful; early oocyte cryopreservation an option if performed early enough; pregnancy counseling required given increased risk of morbidity and mortality
Mixed gonadal dysgenesis	Johansen et al. [40], Flannigan et al. [42]	1 reported case	Infertility considered universal whether reared male or female; 1 successful case of TESE/ICSI
Ovotesticular DSD	Schultz et al. [43], Sugawara et al. [44]	Extremely low 12 cases (females) 1 case (male)	Reared female: rare fertility possible (either spontaneous or with IVF) if internal genitalia appropriate (subfertile) Reared male: 1 live birth after TESE/ICSI

With ART

Surgical Intervention

- Genital Surgery
 - Goal of Genital Surgery
 - Desired Appearance
 - Capacity for Sexual Function
 - Positive Psychosexual Development
 - Good Health-related Quality of Life























Surgical Intervention

- Timing
 - Controversial:
 - Early Surgery:
 - Claims early surgery does not eliminate parental anxiety
 - Legal and Ethical Question of patient autonomy
 - No concrete data that early surgery is beneficial
 - Late surgery
 - Performed once the child identifies gender
 - No Surgery
 - Unless patient consents
 - » Uncertainty on gender
 - » Uncertainty about psychological and sexual development





Shared Decision Making

- Shared Decision Making:
 - A decision is required
 - The best available evidence on risks and benefits options is utilized, reviewed and understood
 - Considers the patient's/family's values preferences
 - Provider offers guidance

Decision Support Tool - Elements

Mandatory		Welcome	
		Your Current Understanding	
		What is DSD?	
		Sex Development Basics	
	 	Support <ul style="list-style-type: none"> • Support for Families • Sharing Information with Others and Reaching Out for Support 	
<i>Mandatory elements must be completed sequentially; Once completed, Tailored and Universal elements may be accessed at liberty</i>			
Tailored to individual patient diagnosis and phenotype	 	Evaluation <ul style="list-style-type: none"> • Evaluation of a Baby with a DSD • Genital / Physical Exams and Medical Photography 	
	  	Testing <ul style="list-style-type: none"> • What Tests are Usually Done First? • Extra Tests • Additional Genetic Testing 	
	 	Your Child's DSD	
	 	Deciding on a Gender of Rearing	
	 	Surgery	
	Universal	     	More Information <ul style="list-style-type: none"> • Well-being Assessments • Parents' Stories • What Have You Learned? • Questions to Ask (question prompt list) • Additional Resources • Glossary

Key:

	Questionnaire assessing knowledge & self-efficacy
	Knowledge/Information provided about topic
	Interactive Decision Support Tool element
	Resources; eg, print-outs, guides, testimonials

Interactive Decision Support Tool

Steps

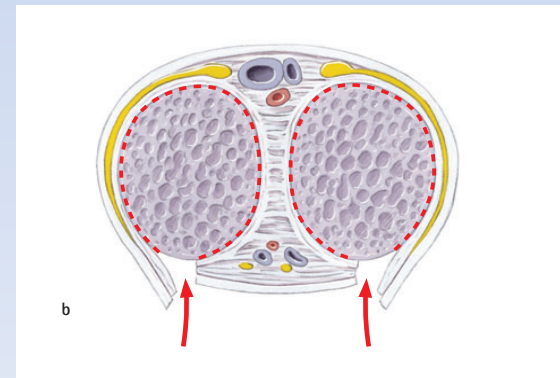
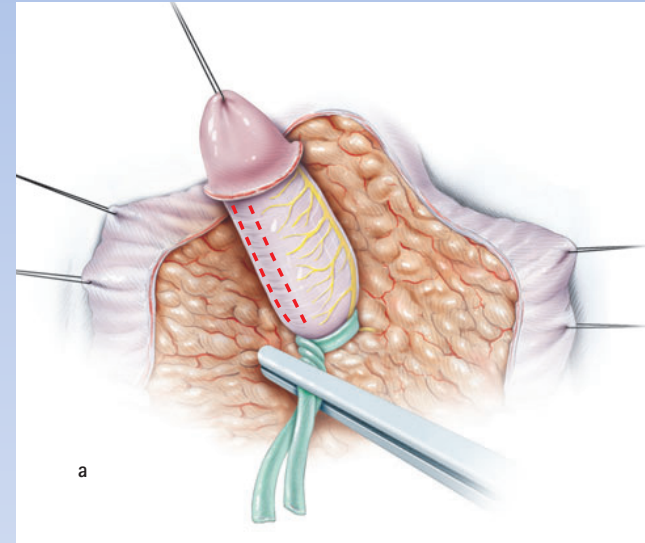
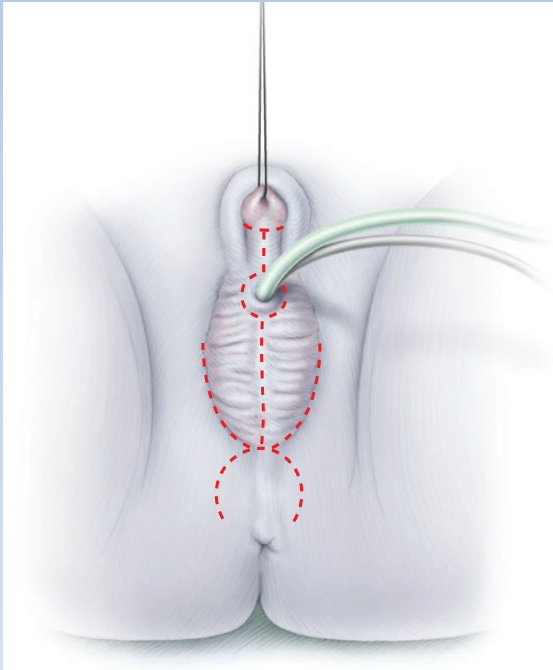
1. Clarify the Decision
2. Explore the Decision
3. Identify Your Decision-Making Needs
4. Plan Next Steps

Components are considered within the steps

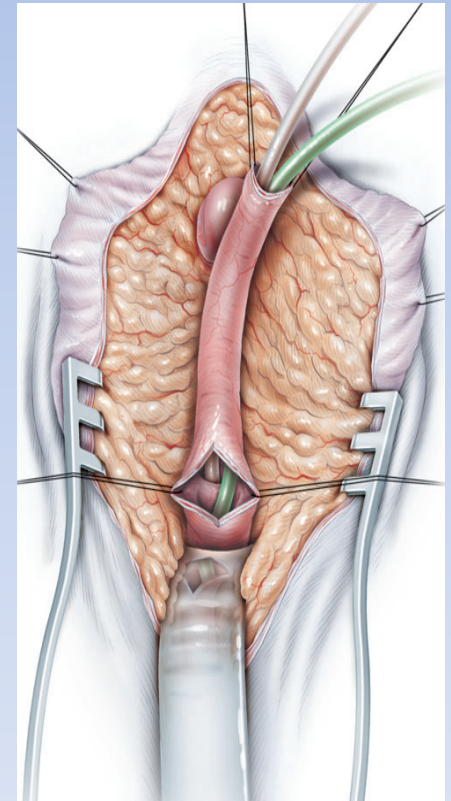
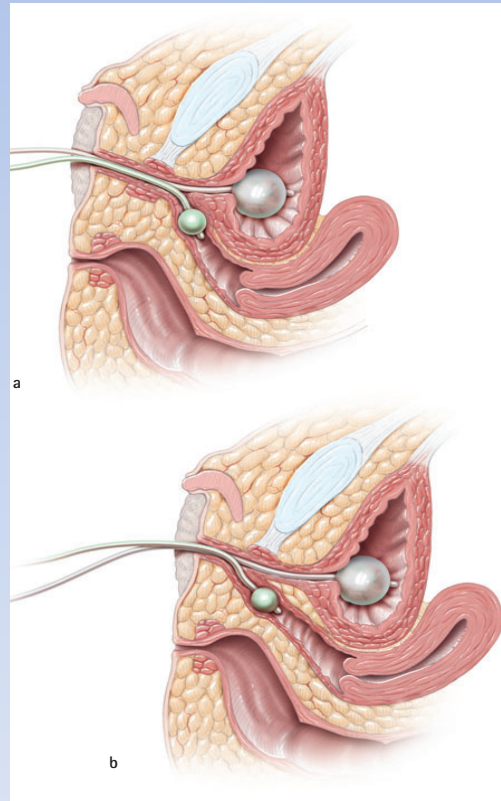
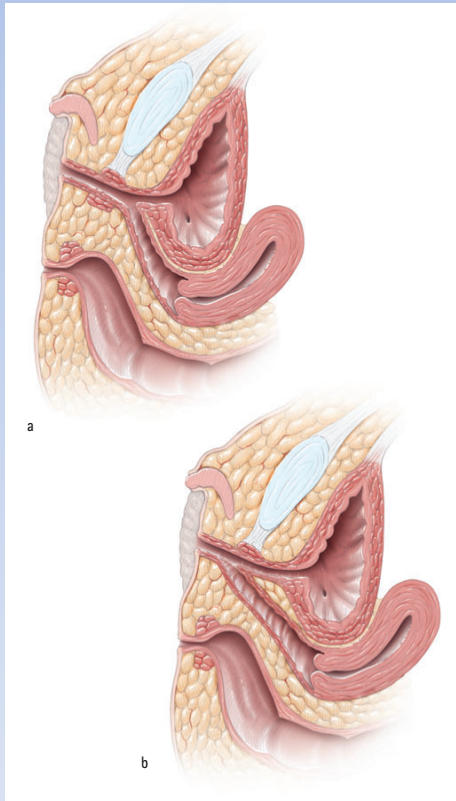
Components

- | |
|-----------|
| Knowledge |
| Values |
| Support |
| Certainty |

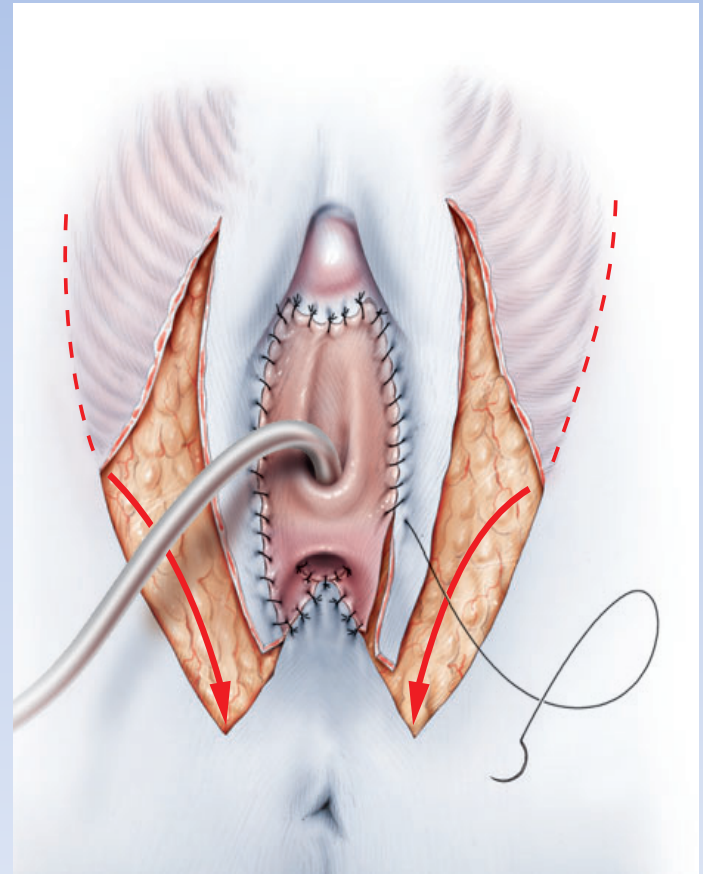
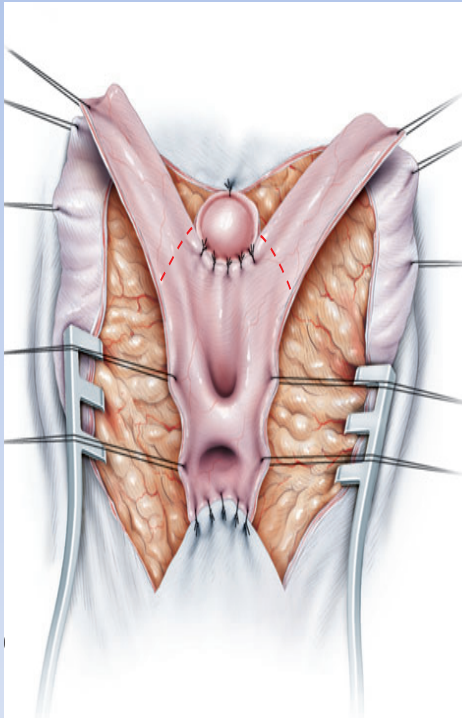
Surgical Repair: Feminizing Genitoplasty

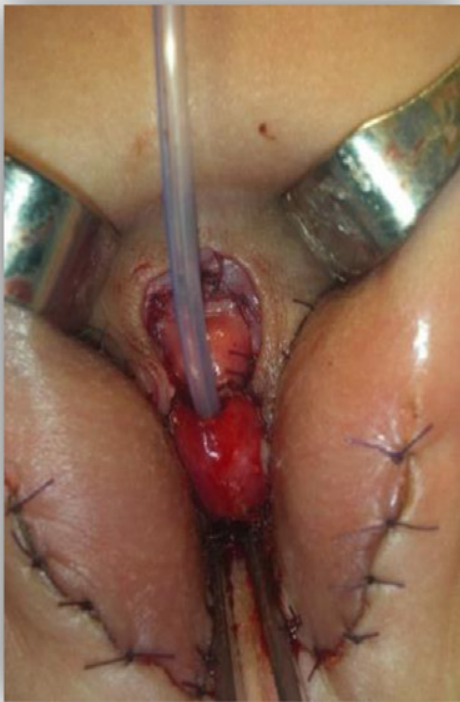


Surgical Repair: Feminizing Genitoplasty



Surgical Repair: Feminizing Genitoplasty





Research

- I-DSD Registry
- I-CAH Registry
- DSD Translational Research Network
- CARES (Congenital Adrenal Hyperplasia)

Groups



AIS-DSD Support Group



**INTERSEX SOCIETY OF
NORTH AMERICA**



BOULDER COUNTY

Gender Support

Open to all gender expansive identities including trans, non-binary, and questioning

LONGMONT GROUP

tuesdays 6:30-8:30pm • 630 main street • longmont, CO 80501

BOULDER GROUP

thursdays 7-9pm • 202 14th street • boulder, CO 80502

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