Disordered Sex Differentiation

DSD has superceded 'intersex' in describing genital anomalies in childhood
DSD results from hormonal imbalances due to (i) abnormal genetic status, (ii) enzyme defects, or (iii) end-organ insensitivity to circulating hormones
Commonest causes are congenital adrenal hyperplasia (#1) and mixed gonadal dysgenesis (#2)
True hermaphrodites = those with co-existent ovarian and testicular tissue
Children with ambiguous genitalia should be investigated and followed up by a specialised multi-disciplinary team. Birth registration and naming of child should be delayed until investigation complete in order that careful consideration be made to gender assignment.

DSD classification

- A. Abnormal gonadal differentiation
  - Klinefelter's syndrome (& mosaics)
  - Turner's syndrome (& mosaics)
  - **Mixed gonadal dysgenesis**
  - 46 XX male
  - 46, XX/46,XY true hermaphrodites
- B. Virilisation of 46XX female
  - **Congenital adrenal hyperplasia** (& subtypes)
  - Maternal androgens
- C. Inadequate virilisation of 46XY male
  - Inadequate MIS activity (deficiency or insensitivity)
  - Failed production of T
  - Failed production of DHT
  - Insensitivity to circulating T

<u>Gonadal dysgenesis</u>

Failed gonadal development, usually due to absent or disordered genetic material
Typically occurs during meiosis (#1 or #2) due to non-dysjunction. Failure of separation leads to one gamete with 22 chromosomes and one with 24. Explains genesis of pure 45 X and 47 XXY karyotypes. Mosaicism results from non-dysjunction during mitosis at blastocyst stage. NB. Dysgenetic gonads at significant risk of subsequent malignancy.

(i) **Mixed gonadal dysgenesis**

- Typically 45X/46XY mosaicism
- Streak gonad one side, testis (often UDT) on other with correponding mullerian and wolffian ducts
- Phallic enlargement but with uterus and vagina
- Usually picked up during investigation for UDT
- Increased risk of gonadal tumours, more commonly involving testis, (gonadoblastoma and dysgerminoma)
- Increased risk of Wilm's tumour - mixed gonadal dysgenesis and Wilm's tumour commonly associatd with Denys-Drash syndrome (triad of ambiguous genitalia, WT and glomerulonephritis)

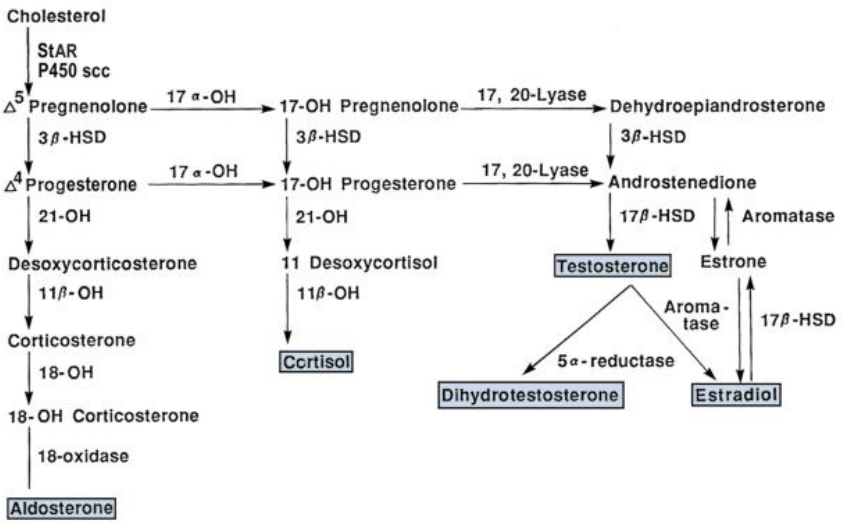
(ii) Turner's syndrome

- Incidence 1:2500

45 X female (occasionally 45X/46XX mosaicism; rarely 45X/46XY but important as high risk of virilisation and gonadoblastoma)
Female sex, failure of secondary sexual differentiation, streak ovaries and primary amenorrhoea
Somatic abnormalities include short stature, webbed neck, increased carrying angle, widespread nipples and short fourth metacarpal
Associated congenital abnormalities include coarctation of aorta, bicuspid aortic valve, horseshoe kidney, duplication or renal agenesis. Multiple renal arteries in 90%
Variant of Turner's known as 46 XX pure gonadal dysgenesis has streak ovaries without other stigmata of Turner's.
Management
- Excision of streak gonad in those with Y chromosome material
- Surveillance for cardiovascular and renal abnormalities

(iii) Kleinfelter's syndrome
Incidence 1:1000 male births
47 XXY (occasionally 48XXXY, 49XXXY or 46XY/47XXY mosaicism)
Occasionally translocation of SRY gene onto an X chromosome results in 46 XX maleness syndrome – very similar to Kleinfelters
Gynaecomastia, female fat distribution, absent facial hair (but often pubic and axillary hair), small firm testes, azoospermia and elevated FSH/LH.
Testosterone low in 50%; occasionally fertile
Phenotype more pronounced proportional to no. of X chromosomes.
Presence of sperm suggests mosaicism
8x increased risk of breast cancer than normal males; also increased risk of Leydig and Sertoli cell tumours
Management
- Careful T replacement
- Reduction mammoplasty if necessary
- Surveillance for breast and testicular malignancy

(iv) True hermaphroditism
46XX (50%), 46XY and 46XX/46XY mosaics remaining 50%
Possess separate gonads or ovotestis



Virilisation of 46XX female

Virilisation of 46 XX female due either to fetal androgen (CAH) or XS maternal androgens (androgen-secreting tumours of ovary or adrenal, maternal treatment with exogenous progestogens)

Congenital adrenal hyperplasia

Responsible for 90% of causes of ambiguous genitalia
Only life-threatening cause - due to severe hyponatraemia
21-hydroxylase deficiency >> 11-beta hydroxylase deficiency > 3-beta hydroxysteroid dehydrogenase deficiency (3B-HSD) > aromatase deficiency
All associated with ACTH-stimulated production of adrenal precursors

(i) 21-hydroxylase deficiency
- 90% cases of CAH
- Incidence 1:15000
- Autosomal recessive
- Mutation of 21-hydroxylase gene on chromosome 6
- 50% salt-losers
- Diagnosis = elevated 17-OH-progesterone
- Management
  - Immediate Mx
    - IV access
    - Bloods for U+E*, 17-OH-Prog, and karyotype
    - Resuscitation with IV saline
    - USS to identify gonads
    - * NB. U+E for 1st 24 hours reflect maternal levels – become hyponatraemic after 24 hours. Therefore do on second day.
  - Longer-term Mx
    - Glucocorticoid and mineralocorticoid replacement
    - Female gender assignment
    - Feminising genitoplasty
    - If pre-natal diagnosis considered in affected families, DXM given to mother from 9th to 17th week aimed at suppressing pituitary-adrenal axis

(ii) 11-beta hydroxylase deficiency
- Rare
- Accumulation of 11-desoxycortisol (more mineralocorticoid action)
- Salt retention and potassium loss, with resultant hypertension
- Severe virilisation

(iii) 3-beta HSD deficiency
- Mild virilisation but severe hyponatraemia
- Accumulation of DHEA and 17-OH pregnenolone

Inadequate virilisation of 46XY male

(i) MIS deficiency or insensitivity
- Normal testis differentiation with T but no descent (intra-abdominal testis), male genitalia and persistence of Mullerian duct structures (large prostatic utricle, ejaculatory duct obstruction, midline prostate cysts, vestigial uterus, fallopian tubes and upper vagina)

(ii) Failed production of T
- Leydig cell aplasia
- Faiure of biosynthesis from cholesterol (e.g. 17-beta HSD deficiency)

(iii) Failed production of DHT
- 5-alpha reductase deficiency
  - Autosomal recessive defect in 5-AR gene (SRD5A2) on chromosome 2
  - Unknown incidence – highest in some Dominican Republic families
  - Undervirilised genetic males
  - Often presents as primary amenorrhoea in 'female' children
  - Testosterone surge at puberty leads to phallic enlargement and testis descent ("female to male syndrome")
  - Rudimentary prostate development due to lack of DHT – never develop BPH or prostate cancer

(iv) Androgen insensitivity syndrome
- Previously testicular feminisation syndrome
- Incidence 1:40,000
- X-linked recessive: Mutation of androgen receptor located on long arm of chromosome X
- Female phenotype with lower 2/3 blind-ending vagina, normal testis and Wolffian duct derivatives. Testis in labia, inguinal canal or abdomen
- Presents with primary amenorrhoea or testis in inguinal hernia in female (vaginoscopy with confirmation of cervix recommended in all females with inguinal hernia)
- Management
  - Orchidectomy
  - Female hormone replacement
  - Vaginal dilatation +/- vaginoplasty
- Partial AIS a/w reduced numbers of AR or reduced affinity for T – Reifenstein's syndrome

Evaluation of ambiguous genitalia

History
- Family history
- Pregnancy history (drugs or illness)

Examination
- Phallus size
- Locaion of urethra
- Labioscrotal folds
- Palpable testes*
- Pigmentation (ACTH)

Blood tests
- Karyotype
- 17-OH progesterone
- U&E

Imaging
- USS (gonads/mullerian duct remnant)
- Genitogram (urogenital sinogram)

Endoscopy

Laparoscopy

Pelvic laparotomy and gonadal biopsy

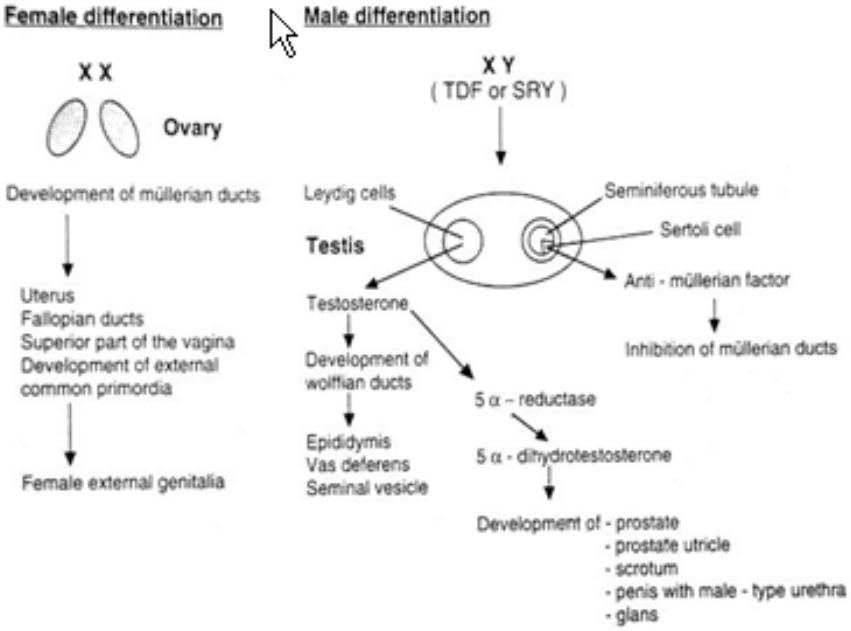
General approach to gender assignment

Delay assignment and birth registration until full evaluation
Once decided avoid ambiguous names
Typically

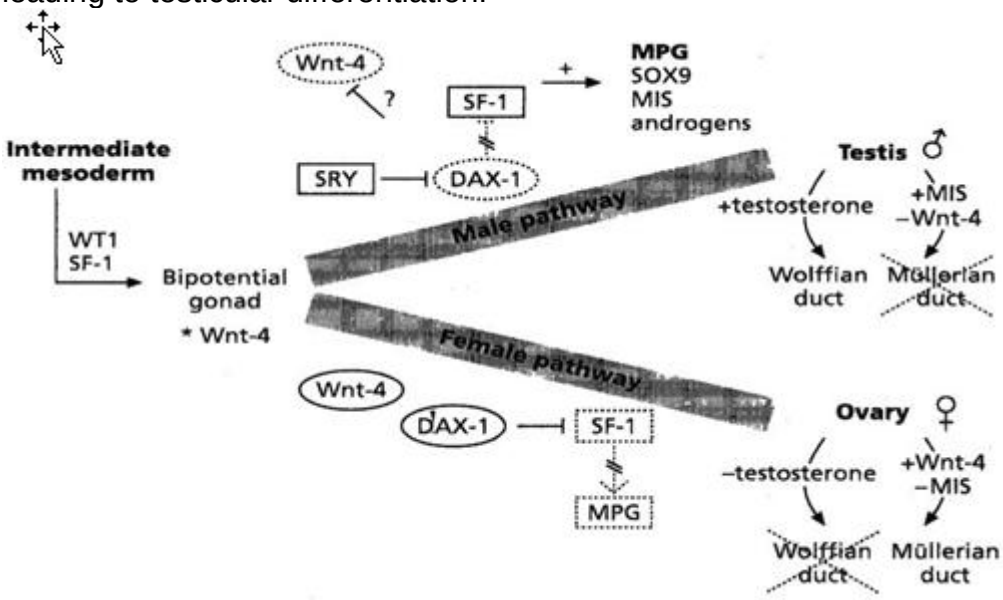
- CAH feminising genitoplasty and female gender
- AIS female phenotype – female gender
  Male pheontype – male gender only if positive T stimulation test
  However it appears that in almost all cases of AIS, patients 'think' like females due to T insensitivity in brain. Therefore female gender assignment is almost universal
- MGD depends on size of phallus

Appendix

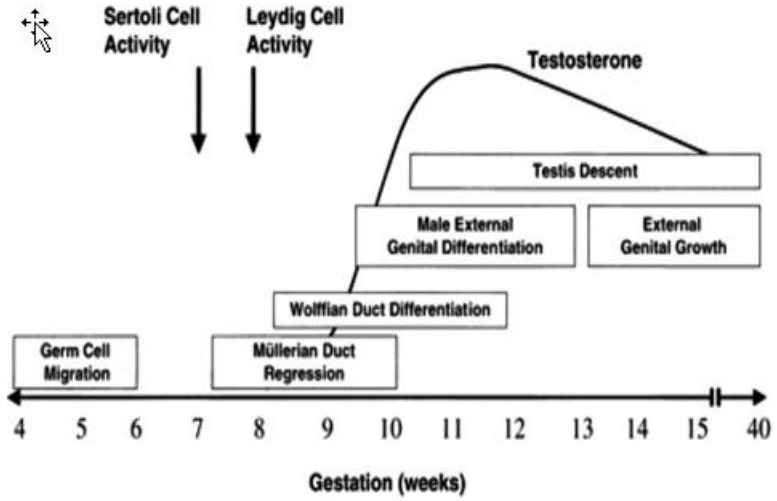
According to the Jost paradigm, three steps must occur for sexual differentiation: establishment of chromosomal sex at fertilization, which determines development of the undifferentiated gonads into testes or ovaries, and subsequent differentiation of the internal ducts and external genitalia as a result of endocrine functions associated with the type of gonad present (Jost et al, 1973).



Testis determining gene (SRY gene,aka TDF) located on short arm of Y chromosome. Downstream genetic cascade includes, SF1, SOX9 and mullerian inhibitory substance, with inhibition of DAX1 (X-related gene) and possibly WNT-4, leading to testicular differentiation.



Sertoli cell activity in differentiating testis leads to production of MIS. MIS resposnsible for stimulating Leydig cells to produce T and also guides first phase of testicular descent. T stimulates Wolffian duct development into epididymis, vas and seminl vesicles. Peripheral conversion of T to DHT by 5-alpha reductase leads to deveopment of prostate and external genitalia.



As implied by Turner's syndrome, the presence of two functioning X chromosomes required for normal female differentiation – otherwise gonadal dysgenesis occurs