Newborn and child: Disorders of sex development

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Prevalence DSD

- **Genital anomalies**

  1: 4 500 births

  (Thysen, U. et al., Horm.Res., 2006)

DSD

„disorders of sex development“

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

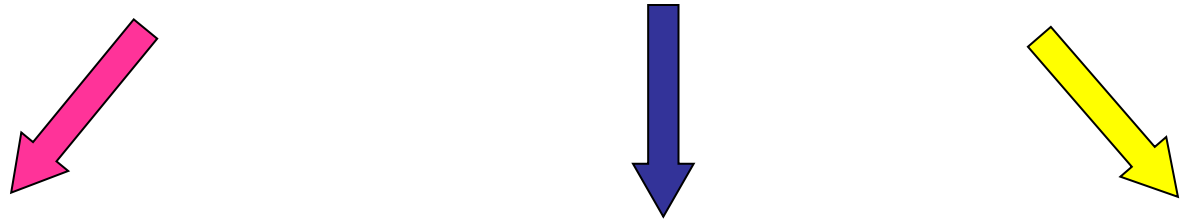
DSD

- Most cases recognised in **neonatal period**

- **Later presentation**:

- Previously unrecognised genital ambiguity
- Inguinal hernia in girls (46, XY CAIS)
- Delayed or incomplete puberty
- Virilisation in girls
- Primary amenorrhea
- Breast development in boy
- Occassionally cyclical haematuria in a boy

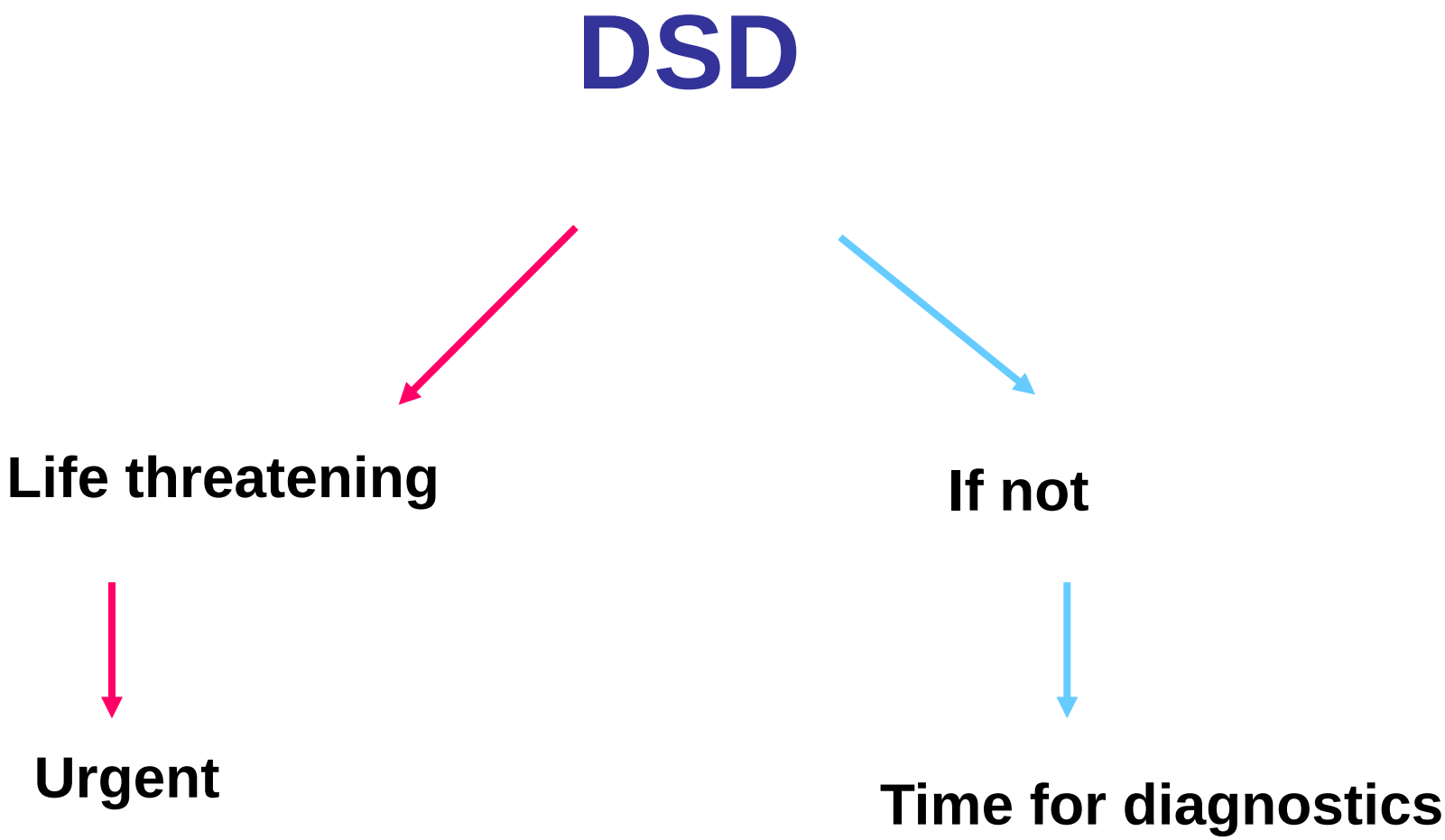
DSD



Female
XX

Male
XY

?


DSD
Life threatening
If not
Urgent
Time for diagnostics

Approach to the problem 1

- **History** (family history of ambiguous genitalia, maternal health including virilisation), drugs during pregnancy, previous stilbirths or neonatal deaths…)

- **Examination** (dysmorphic features of midline defects, hydration, blood pressure)

Approach to the problem 2

Genitalia

- **Palpable gonads?** (if yes: likely to be **testes** – normal or dysgenetic or ovotestes)
- **Degree of virilization** (Prader)
- Measure the **length of the phallus** stretched length from pubic tubercle to tip of penis). **Normal**: about 3 cm, micropenis <2-2.5 cm (ethnic origin).
- Position of the **urethral opening**, **vaginal opening, urogenital sinus.**

Approach to the problem 3

- Appearance of **labioscrotal folds, rugosity.**
- Note the **pigmentation of genital skin** (excessive ACTH and opiomelanocortin in CAH).
- Determine the **baby´s gestation** (preterm girls, in boys usually testes undescended until 34 weeks).

Investigations 1

- FISH or PCR for Y and X chromosomes.
- Blood karyotype, mosaicism?
- Blood electrolytes.
- Blood sugar.
- **Anatomy** of internal genitalia.

  establishing whether **testes** are capable of producing **androgens.**

Investigations 2

- T and hCG test.
- LH, FSH and GnRH test.
- ACTH test (17-OHP,DHEAS, A-dion, T, DOC…)
- Determining of internal anatomy (Prader stages I-V, Quigley stages).
- Ultrasound scan (anatomy of urogenital sinus/ vagina/uterus/renal anomalies).
- Urogenital sinogram.

Investigations 3

- Cystography, laparoscopy with or without biopsies of gonads and skin.
- MRI scan of the pelvis.

Ambiguous genitalia in newborn

1. **Exclude congenital adrenal hyperplasia (CAH) !!!**

- **Monitoring:** 17-OHP, Na+, K+, glycaemia, cortisol

- **Karyotype**

2. **If CAH is not confirmed:**

- Laboratory examination.
- Ultrasound scan (adrenal glands, ovaries).
- DNA analysis …

Investigations: newborn with ambiguous genitalia

- **Karyotype:** blood/FISH/PCR
- **Electrolytes** (Na+, K+, Cl-)
- **Blood sugar** (hypoglycaemia: cortisol deficiency)
- **Pelvis USS** (U and O normal)
- **Plasma 17α-OHP** (take sample before any steroid given !!!),
- **optimal timing:** after 48 h of life (clearance of placental production, subsidence of postnatal surge in infant…)
- **Steroid profile** (urine or blood)
- **Blood** for CYP21 gene analysis

Clinical presentation of CAH

- **Ambiguos genitalia in females** (21-OHD) **or males** (3 ß-OHSD, 17 α-HSD, 17 ß-HSD)
- **Pigmentation** of the genitalia (excess of ACTH production)
- **Salt-losing crisis: sufficient cortisol unless stressed**
- **Over 90% of CAH: 21-OHD (↑17α-OHP)**

Rarer causes of CAH

- 11ß-OHD: **hypertension and ambiguous genitalia** in female (excess of T and DOC – not present in newborns), in male enlargement of penis.

- 3 ß-OHSD: **adrenal failure and severe salt loss** (aldosterone deficiency) – high mortality in infancy, virilisation in girls and low virilisation in boys.

Management CAH 21-OHD: newborn1

- Start **hydrocortisone.**
- **Salt** (oral solutions or salt tablets dissolved in 1 ml water).
- Assess **blood electrolytes** 3 days – early identification of salt loss.
- **1st sign of aldosterone deficiency**: **K+ rise** in plasma (to precede Na+ fall).

Management CAH 21-OHD: newborn 2

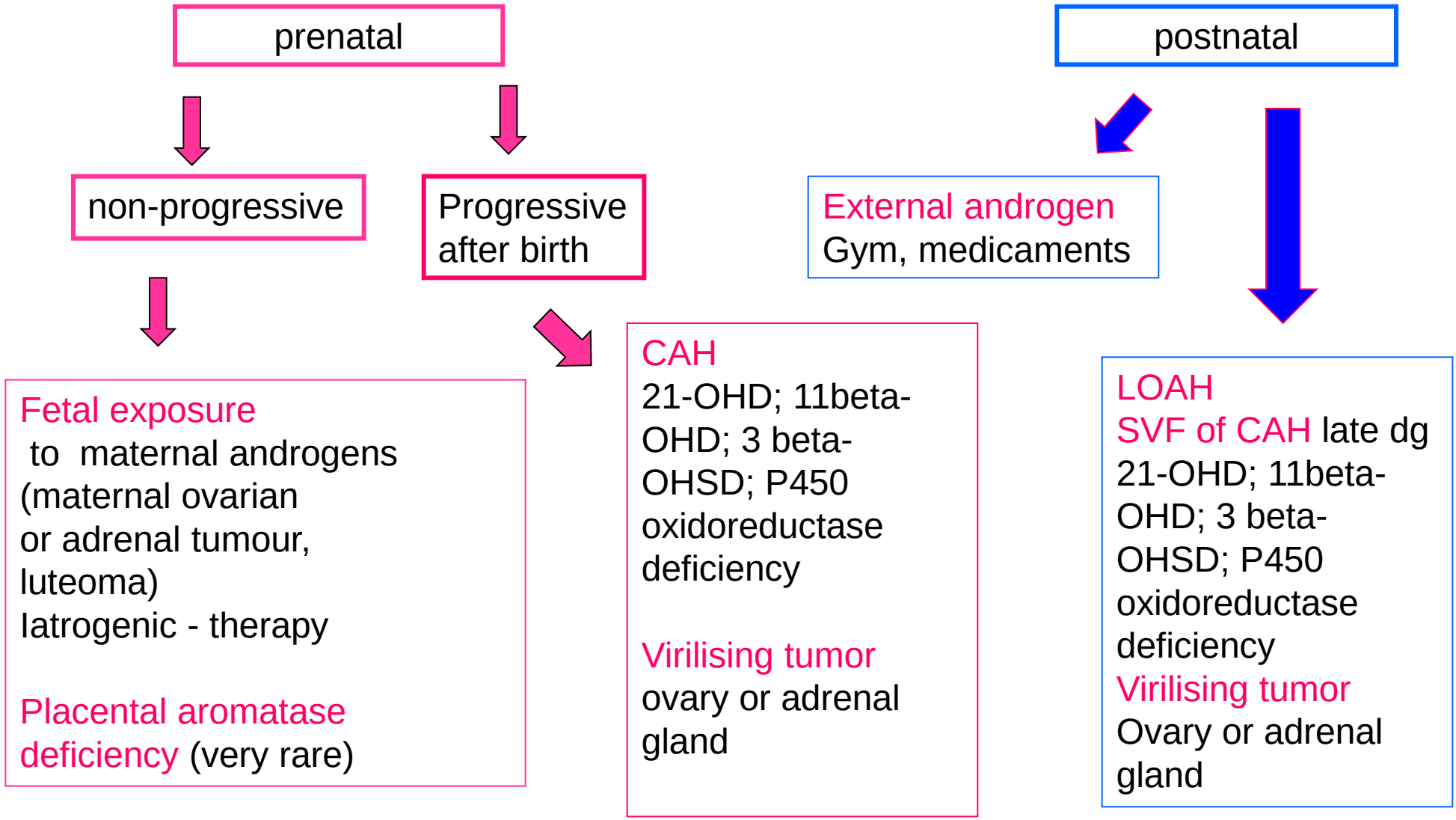
- **If: ↑K+ or ↓Na+:** take a **blood sample for Aldosterone and PRA.**
- Start 9α-fludrocortisone 25 µg b.d. increase to 50 µg b.d. if Na+ remains low.
- To give **salt supplements** (5 mmol/kg/day).
- FLUDROCORTISONE IS NOT EFFECTIVE WITHOUT SUFFICIENT SALT REPLACEMENT.
- Regular follow-up by endocrinologist.

Home management CAH 21-OHD

- Care of a paediatric endocrinologist.
- Hydrocortisone treatment & Fludrocortisone & salt.
- Instructions to parents what to do in the case of illness (to doble or trible hydrocortisone), intramuscular injection …
- Neonatal screening: detection 21-OHD only.
- Cut off: maturity of newborn, age at blood sample, methods.
- *Antenatal treatment in females* (?).

CAH excluded

Female, 46 XX virilising DSD



Investigations in female newborn with ambiguous genitalia

- **Karyotype:** blood/FISH/PCR
- **Electrolytes** (Na+, K+, Cl-)
- **Blood sugar** (hypoglycaemia: cortisol deficiency)
- **Pelvis USS** (U and O normal)
- **Plasma 17α-OHP**
- **Steroid profile** (urine or blood)
- **Blood** for CYP21 analysis

Differential diagnosis in 46, XY

- Gonadal dysgenesis/malfunction
- Biosyntetic defect
- End-organ unresponsiveness
- Syndromes, Smith-Lemli Opitz, Denis Drash etc.)

Investigation and management of DSD 1

- **Gender assignment:** expert evaluation in newborns.
- **Evaluation and long term management:** at a centre with an experienced multidisciplinary team.
- **Open communication** with patients and families is essential.
- **Patients and family concerns** should be respected and addressed in strict confidence.

Investigation and management of DSD 2

- Reassurance of parents.
- Registration of birth after sex of rearing determination.
- **Before assigning sex searing (male to female):**

  to **assess the effect: i.m. T** or DHT cream on penile growth
  to help anticipate the response in puberty.