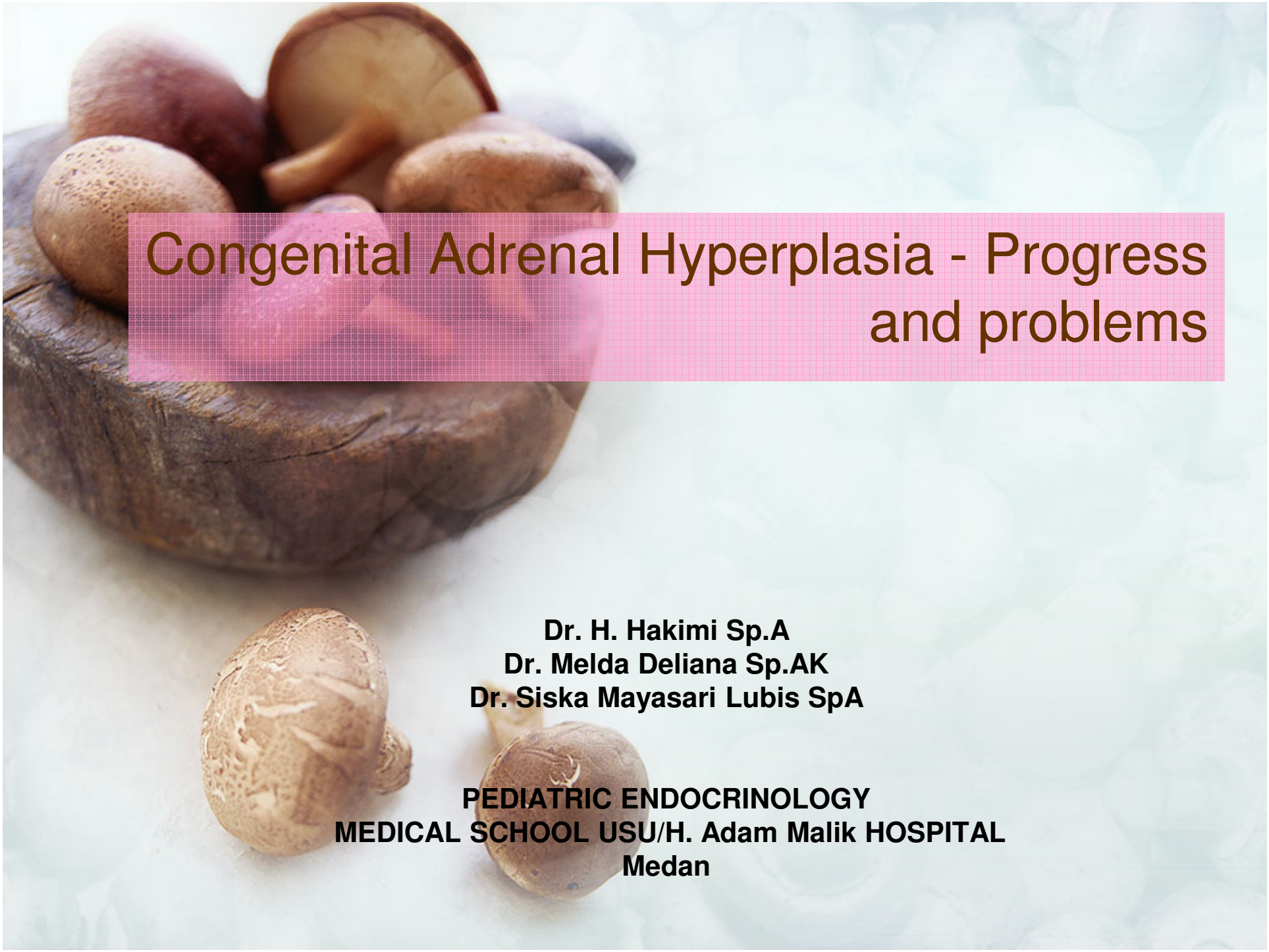

Congenital Adrenal Hyperplasia - Progress and problems

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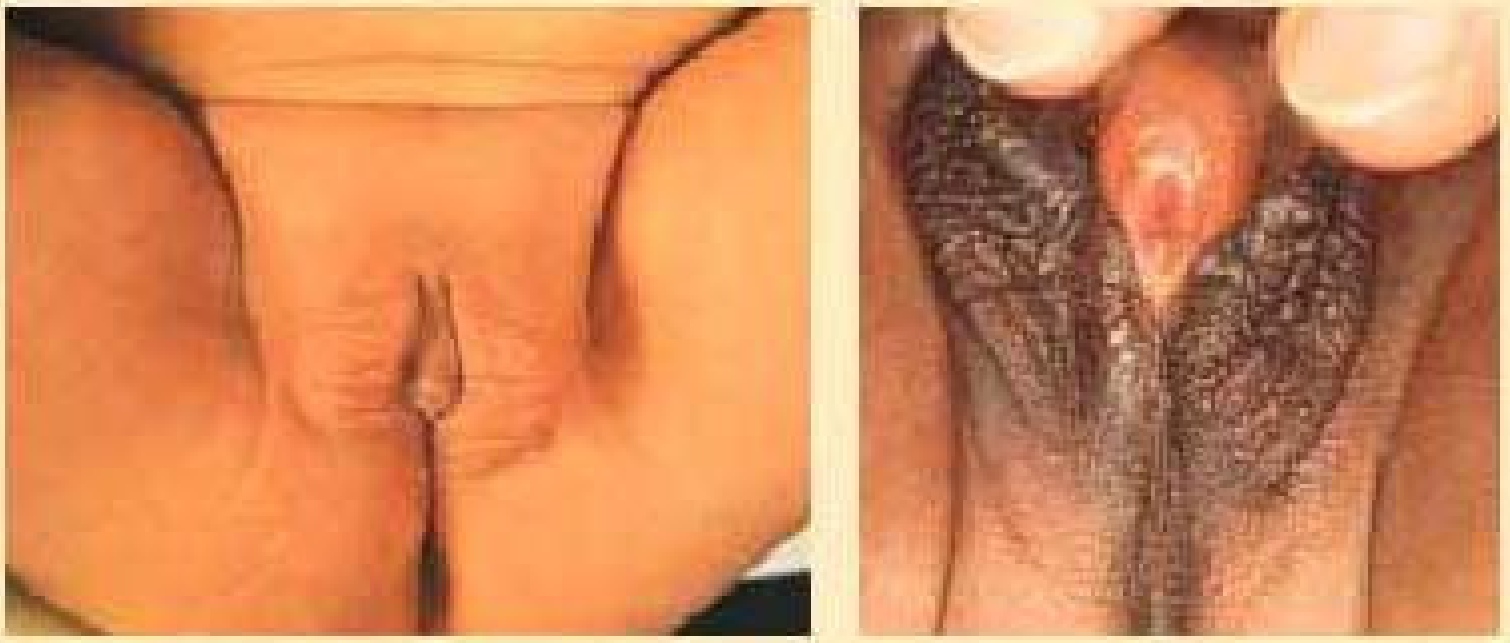
Objectives

- Describe the problems of CAH
- Describe the current situation in Indonesia
- Conclusion

Epidemiology

- Incidence 1:15000 (global)
- Autosomal recessive
- most common cause of
  - **ambiguous genitalia**
  - **female pseudohermaphroditism (FPH)**
- Clinical manifestation
  - **Classic (*salt losing and simple virilising*)**
  - **Non-classic (*late onset*)**

Ambiguous Genitalia - Infant



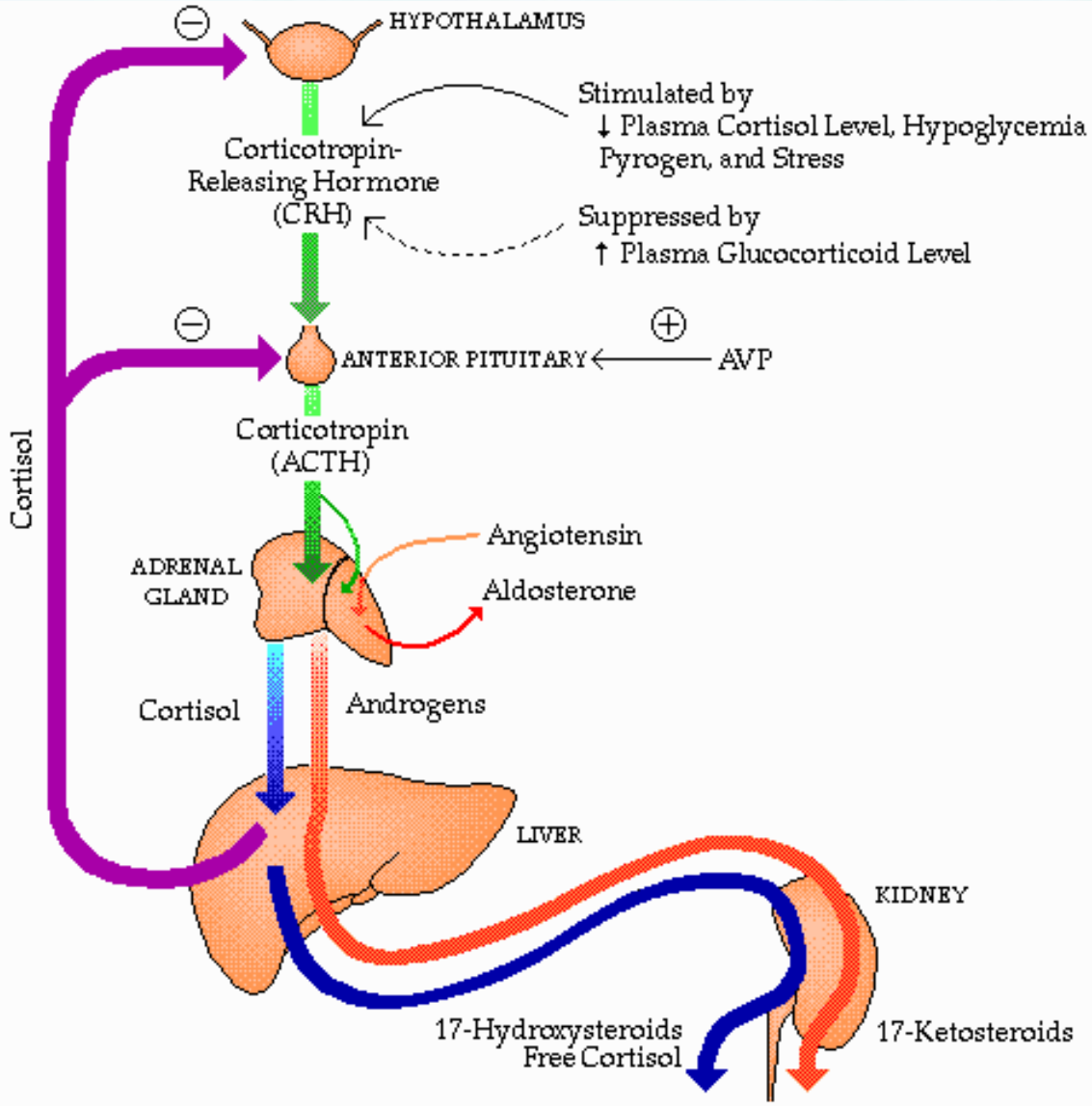
Rugation ("scrotalization") of the labia majora and clitoromegaly are evident in a newborn girl with documented virilizing CAH resulting from 21-hydroxylase deficiency (left). Another newborn with the same condition exhibits posterior labial fusion as well as rugation and clitoromegaly (right).

Heterosexual Precocity

- 46, XX
- Early signs of puberty
- Virilism

➔CAH

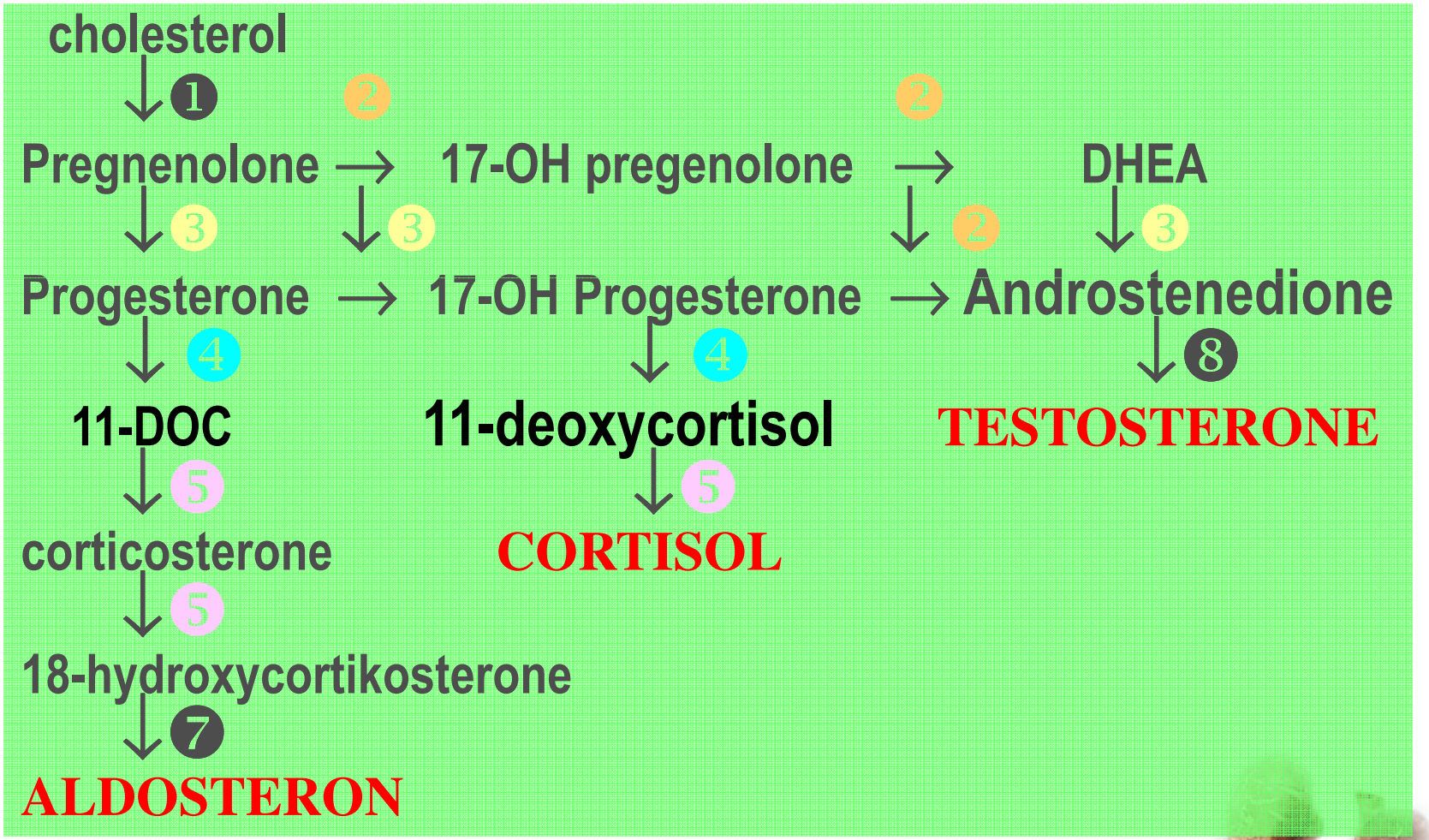
ADRENAL AXIS



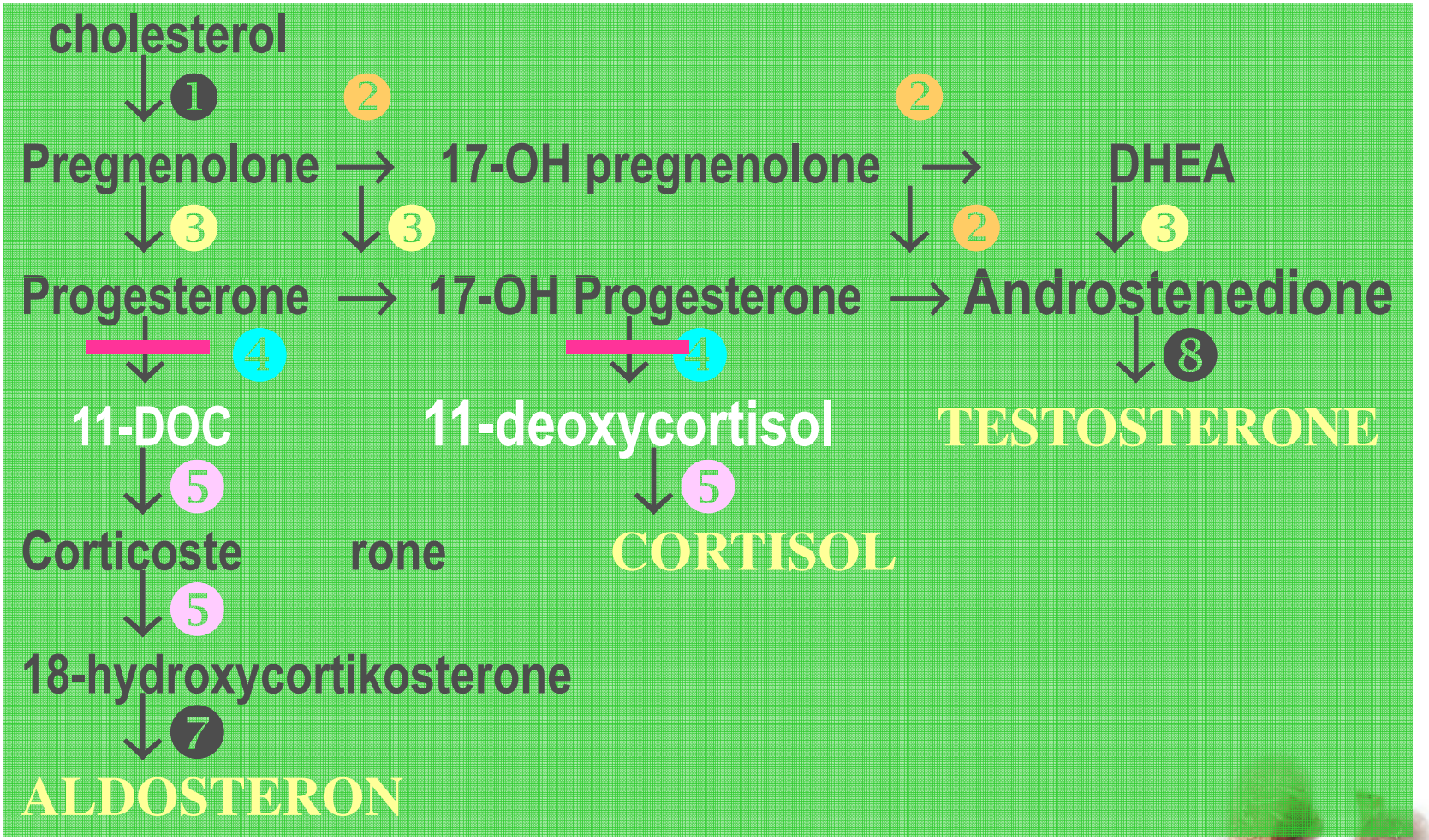
Adrenal steroid enzymes

Enzyme	Location	Chromosome
❶P450scc	Mitochondria	15q23-24 (CYPscc)
❷P450c17	Endoplasmic reticulum	10 (CYP17)
❸3βHSD	Endoplasmic reticulum	1p11-13
❹P450c21	Endoplasmic reticulum	6p21.3 (CYP21B)
❺P450c11β	Mitochondria	8q21-22 (CYP11B1)
❺P450c18		8q21-22 (CYP11B2)

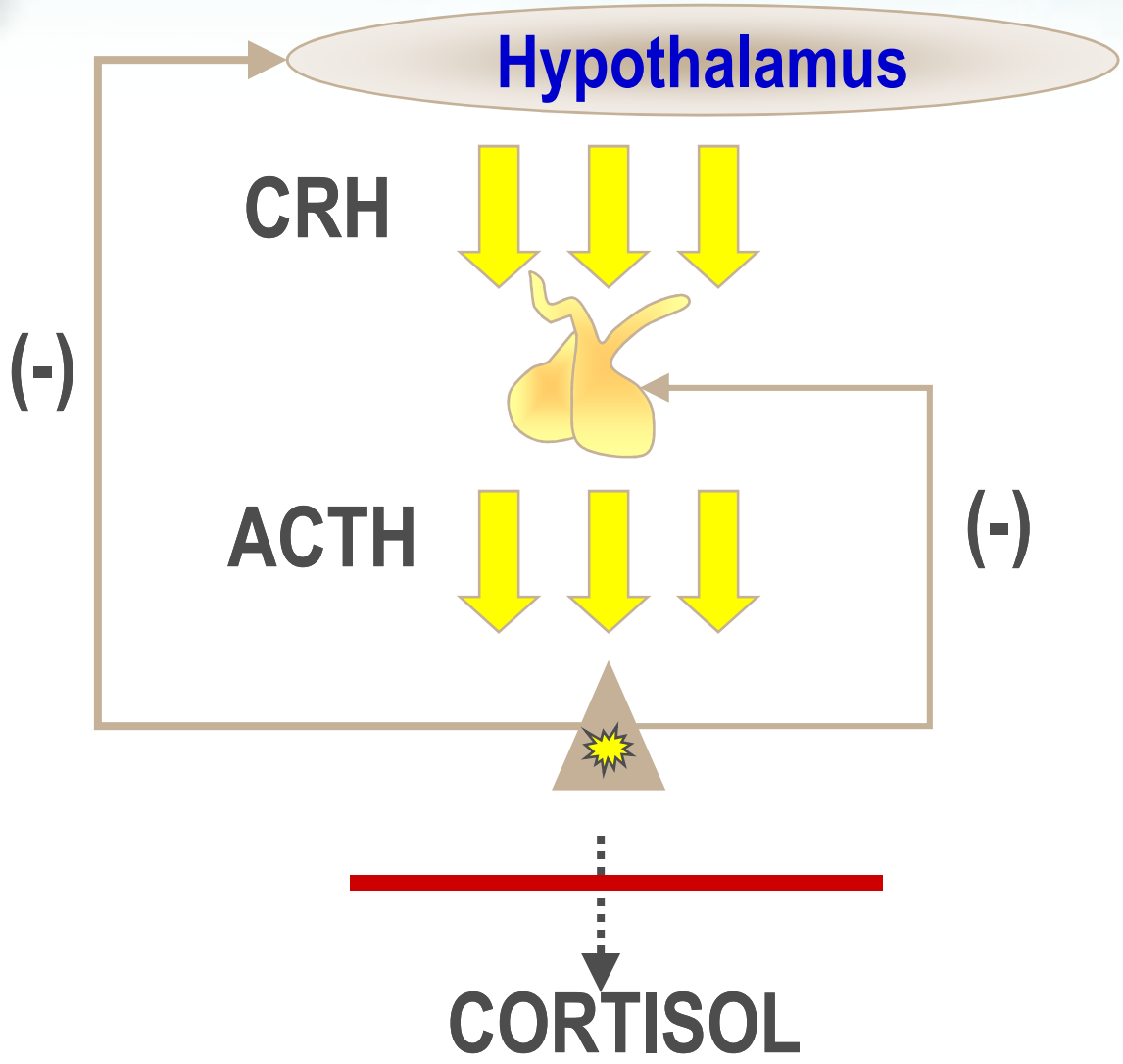
Adrenal steroid synthesis



CYP21 deficiency



Adrenal axis in CAH



Mechanism of disease

- enzyme defect **of the adrenal cortex → disruption in steroid biosynthesis → cortisol deficiency → Addison crisis prone**
- **compensatory increase of androgen secretion → virilisation**
- **mineralocorticoid arm affected →decrease aldosterone → electrolyte imbalance (sodium loss)**
- **decrease androgen secretion → undervirilised male**
- **increased deoxycorticosterone production → hypertension**

Clinical Manifestations

Enzyme defect	MPH	FPH	Salt losing	Hyper tension
P450scc	+	-	+	-
CYP21	-	+	+	-
CYP11	-	+	-	+
3βHSD	+	+	+	-
CYP17	+	-	-	+

Classification -Salt Wasting

- Enzyme activity 0-1%
- life-threatening metabolic crisis
  - **presenting in the first weeks after birth**
  - **salt-loss (hyponatremia) and hyperkalemia**
  - **dehydration and shock**
- failure to thrive
- ambiguous genitalia in females but not in males.

Classification -Simple Virilizing

- Enzyme activity 1-2%
- Clinical
  - **Precocious puberty - gonadotropin independent**
    - female: heterosexual variable degree of clitoris hypertrophy and posterior labial fusion
    - male : isosexual
  - **Without salt wasting**

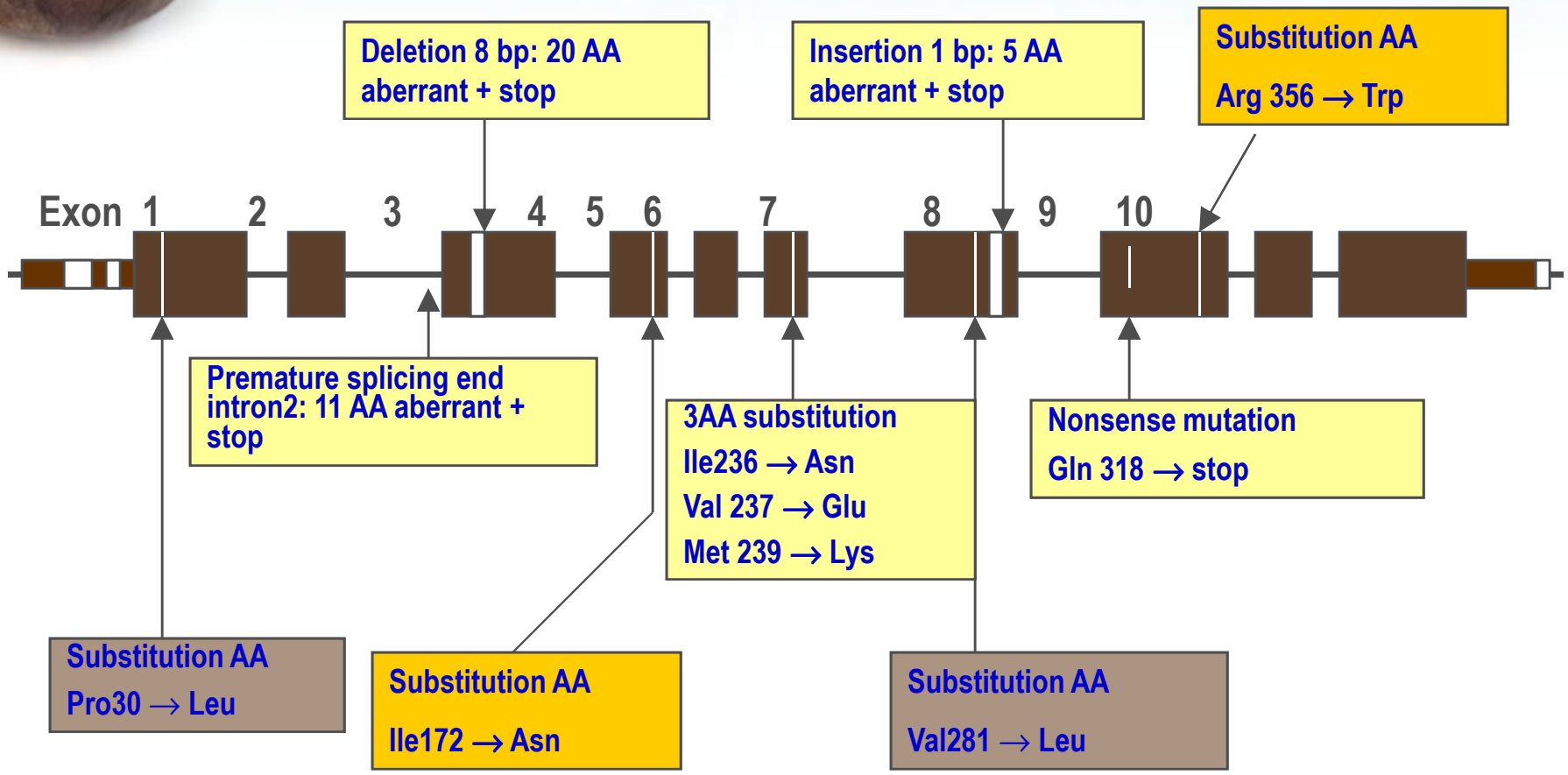
Classification-Non classical

- Enzyme activity 20-50%
- rarely diagnosed before puberty
- hirsutism: CYP21 9%; 3βHSD 17%; CYP11 6.5%
- premature adrenarche/pubarche: CYP21 6.6%; 3βHSD: 10%
- Intersex male: 46,XY female
- hypertension in children and young adults

Mutations in CYP21 classic CAH

Mutation	Location	Frequency (%)
Deletion	CYP21	25-30
Pro30Leu	Exon 1	5-10
A(C)656G	Intron 2	20-25
8bp	Exon 3	5-10
Ile172Asn	Exon 4	5-10
Exon6 cluster	Exon 6	5-10
Val281Leu	Exon 7	5-10
1757+T	Exon 7	< 5
Gln318Stop	Exon 8	5-10
Arg356Trp	Exon 8	10

Genotype Phenotype correlation



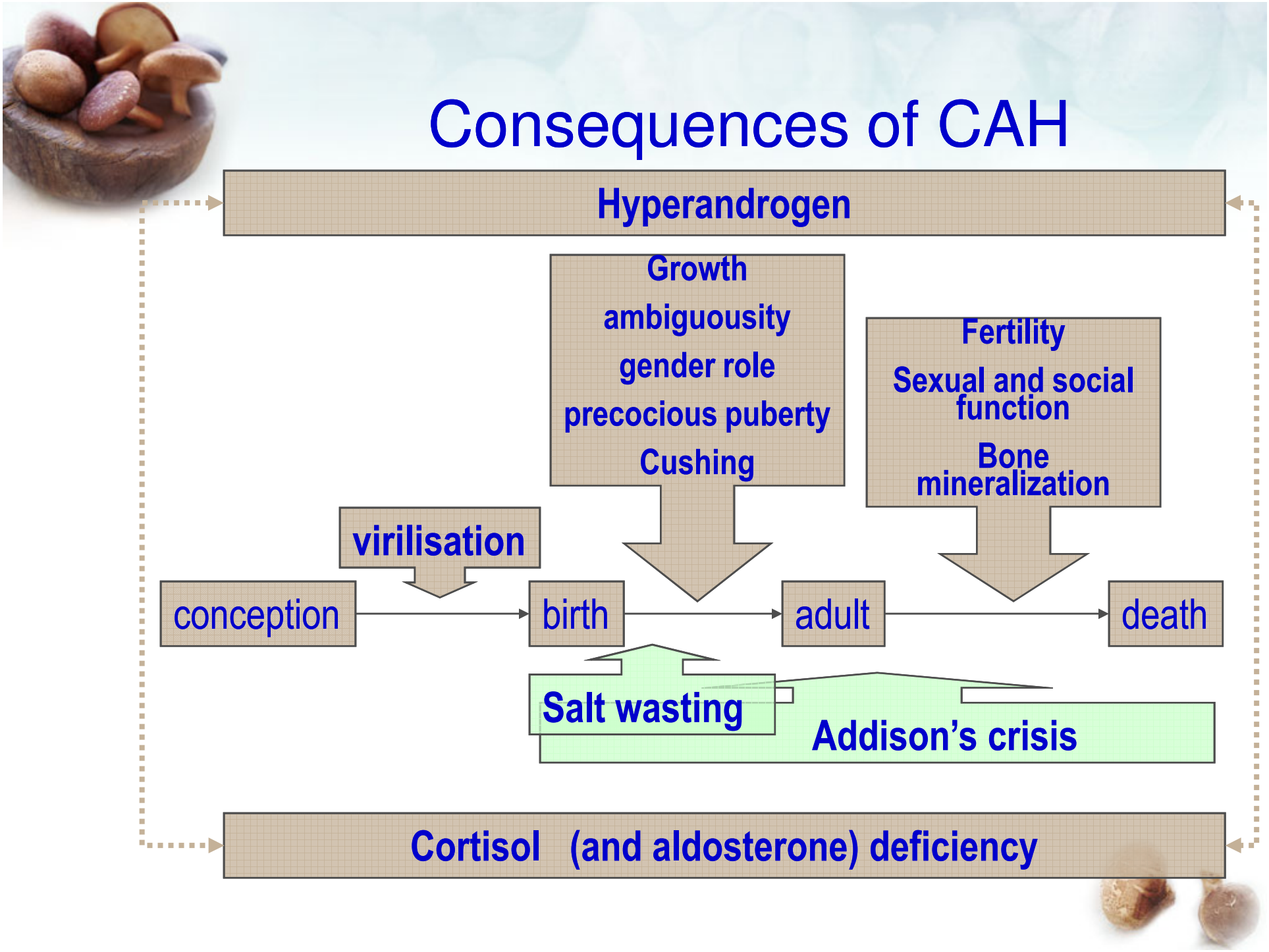
Diagnosis - clinically

- salt wasting episode of the newborn
- failure to thrive in young infants
- ambiguous genitalia
- intersex case
- hypertension in young age
- hirsutism and menstrual irregularities
- PCOS

Diagnosis - laboratorium

- Hormonal
  - **depend on the affected pathway**
  - **urine, blood, saliva - 17 OHProgesterone**
- Metabolic - Addison crisis
  - **hyponatremia, hyperkalemia**
  - **hypoglycemia**
  - **metabolic acidosis**

Consequences of CAH



Management - objectives

- Prenatal
  - **avoid virilisation of affected female**
  - **avoid surgery**
- Postnatal
  - **avoid adrenal crisis**
  - **normal growth and development**
  - **surgery - clitoroplasty and vaginal reconstruction**
  - **psychology**
  - **genetic counseling**

Management - Prenatal (1)

5 weeks

Mother's serum estriol

R/ DEXAMETHASONE 0.5 mg bid/tid

8 weeks

Mother;s Blood glucose every 2 months and serum estriol per month

9 weeks

CVS

Karyotyping & analysis HLA/21-OH/C4

-boy/normal female: stop R/

-affected female: continue R/

or

10 - 11 weeks

CVS + amnio

amnio

Monitor serum 17-OHP, androstenedione, T

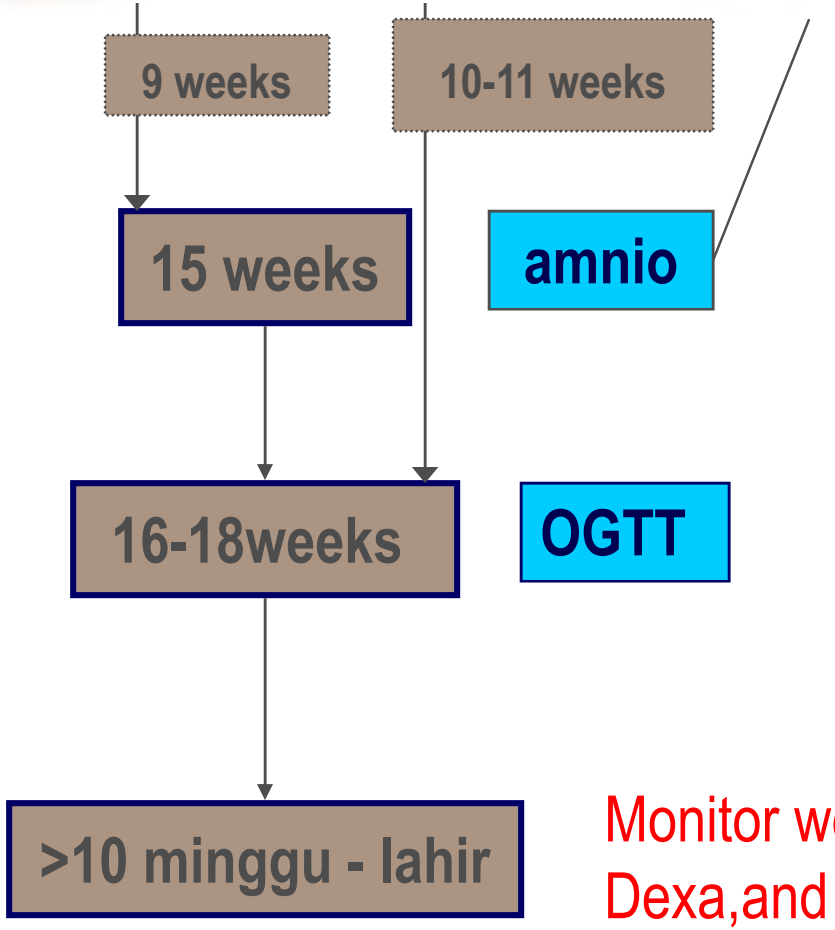
analysis HLA/21OH/C4 for suspected cases

Continue……

PTO

continued

Management - Prenatal (2)



Monitor weight,BP, fasting BG, side effects of Dexa,and serum estriol. Repeat OGTT

Management - *replacement*

- Prenatal → dexamethasone (0,5 – 2 mg/day)
  - **since early pregnancy (early sexual development)**
  - **Unbound to high affinity protein**
  - **Not metabolized by placental 11-hidroxysteroid dehydrogenase**
- Postnatal → hydrocortisone (15 - 25 mg/m2/day)
  - **life long treatment**
  - **increase dose (3x) in illness / stress situation**
  - **use the minimum effective dose, least growth retarding effect steroid in children**
  - **adult may switch to dexamethasone for complianc**

→ fluodrocortisone (0,05 –0,1mg/day)

Surgery

- Clitoroplasty
  - **before gender role established**
- Vaginal reconstruction
  - **before sexually active**
  - **before marriage**

Problems of CAH

- Diagnosis
  - **intra uterine**
  - **extra uterine**
- Management
  - **medicine**
  - **surgery**
  - **psychology**

Problems of CAH

- Prognosis
  - **adult - most short normal, obese**
  - **fertility**
  - **sexual functioning**
- Social emergency ➔
  - **birth: gender**
  - **Gender role**
  - **Adult self esteem**
- Medical emergency ➔ Addison crisis

PRENATAL TREATMENT

- Success 75%
  - 1/3 normal genitalia
  - 2/3 mild virilization
- Failure
  - Inadequate dosage
  - Interruption of treatment
  - Delay in initiating treatment
  - Variability in maternal metabolic clearance
  - Variability of placental metabolism of the administered glucocorticoid

PRENATAL TREATMENT

- Adverse reaction
  - **Maternal** (1/3 of treated mothers)
    -edema, excessive weight gain, irritability,mood swings,nervousness, hypertension,glucose intolerance,-chronic epigastric pain, gastroenteritis,Cushingoid, hirsutism, severe striae
  - **Fetal**
    -sponataneous abortion,IUGR,liver steatosis,hydrocephalus, agenesis corpus callosum, hypospadia, cryptorchidism.
- **Not considered a direct cause of dexamethasone**
- **1/3 treated mothers not electing treatment for next pregnancy**

(American Academy of Pediatrics, 2000)

Adult height

- CAH
  - **untreated → adult height -6SDS**
  - **increase androgen → bone age acceleration ("tall child") → early epiphyses fusion ("short adult")**
  - **overtreatment → steroid induced growth suppression**

delicate dosage balancing

regular growth monitoring

alternative protocol

Adult height – Eugster et al (2001)

- Own institution (N=65)
  - **Final height -1.03 SDS (N=23)**
  - **¼ males & 1/3 females final height -0.5 SDS**
- Metanalysis (N=561)
  - **Final height - 1.21 SDS**

early diagnosis
good compliance → **Better final height**

Failure of adrenal suppression

- Hyperresponsivity of adrenal to ACTH
- Abnormal steroids
  - **Resistance to glucoscorticoid and mineralocorticoid**
- Redundancy of mechanisms governing ACTH release
  - **ACTH release not only by CRH, but AVP, interleukins 1,2,6 TNF-alfa, galanin, prostaglandin**

(Van Wyk and Gunther, 1996)

Alternative treatment

- Adrenalectomy (Gunther et al, 1997)
- Alternative regiment 1 (Merke et al,2000)
  - **androgen blocking agent (flutamide)**
  - **Aromatase inhibitor**
  - **enzyme responsible for estrogen formation from androgens (testolactone)**
  - **low dose hydrocortisone**
- Alternative regiment 2 (Levine, 2000)
  - **With GnRH analogue**

Fertility - Male CAH

- Cabrera et al (2001) → 18 / 30 adult with testicular sonogram
  - **50% Salt waster; 50% Simple virilising**
  - **Presence of adrenal rests within testes**
    - more frequent in Salt losing
    - increases risk of fertility

Fertility - Female CAH

- Decrease fertility:
  - **abnormal genital anatomy, vaginal stenosis**
  - **Hyperandrogenisme ➔ diminished ovulation.**
- Delivery generally ➔caesarian section
  - **vaginal stenosis**
  - **androgenic pelvic girdle.**

Fertility - Female CAH

- Federman (1992) → N =80
  - **Normal menses: SV 55%; SL 67%**
  - **Fertility ratio: SV 60%; SL 2.5%**
- Premawardhana et al (1997) → N=16
  - **Normal menses:SV 75%; SL 64%**
  - **1/3 hirsutism**
  - **Ovulation rate 40%**
  - **Fertlity rate 60%**

Gender role

- Preference for playing with boys 82%
- Masculine sport in adolescence 70%
- Masculine gender role continues into adolescence and aulthood

(Slijper et al, 1992)

•Increased masculine behaviour in CAH girls

(Hall et al, 2001)

•Masculine behavior due to prenatal androgen exposure and not in postnatal life

(Berenbaum et al,2000)

Sexual functioning

- Low sexual activity (10%)
- Sexual orientation – heterosexual
- Masturbation – 70%

(Slijper et al, 1992)

- Premawardhana et al (1997)
  - **Reconstructive surgery 94% (50% require 2nd)**
  - **Adequate vaginal introitus 77% → sexually active SV 75% and SL84%**

BONE MINERAL DENSITY

- Bone mineral density (BMD)
  - **increased by excess androgen exposure**
  - **decreased by excess glucocorticoid exposure.**
- Whole-body BMD - adult
  - **no difference between patients with CAH and control**
  - **men with CAH had lower spinal BMD scores when compared with unaffected men.**

Problems in Indonesia -diagnosis

- Dept of Child Health Jakarta (hospital data) - 1993
  - **20 patients mean age of diagnosis 33 months (7days - > 9 years old)**
  - **Salt wasting 40%**
  - **sex ratio 19 female and 1 male**
  - **increased serum 17-OHP: 20**

Problems in Indonesia -diagnosis

- Dept of Child Health Jakarta (hospital data) - 1993
  - **most common chief complaint: virilisation / clitoromegaly**
  - **Referral: 1 by midwife, 3 by general physician, others (pediatrician, ObGyn, pediatric surgeon)**

Underdiagnosed / misdiagnosed

Problems in Indonesia -therapy

- Hydrocortisone
  - **availability: only in big city and certain pharmacist**
  - **oral : powder form**
- Fluodrocortisone not available
- Surgery
- Psychology Counseling
- Compliance

Problems in Indonesia - monitoring

- Monitoring (17-OHP & PRA)
  - cost
  - availability
- Alternative
  - **clinical: growth, signs of virilisation or puberty, bone age**

Unsatisfactory result

Team work

- Geneticist, biochemist, psychology, obstetrician, internist, radiologist, surgeon, molecular biologist and pediatric endocrinologist

Conclusion

- Medical and social emergency
- Growth and development of child
- Adult: short final height, fertility, and social consequences
- Current management still needs improvement
- Team work is essential
- Alternative management →research

THANK YOU